ATP7B Gene Analysis in Wilson Disease

Clinical Features:

Wilson disease is an autosomal recessive disorder characterized by excessive copper accumulation in various organs, primarily the liver, brain, kidney and cornea and can present with hepatic, neurologic or psychiatric abnormalities or a combination of all these. The clinical course is highly heterogeneous and age of onset ranges from 2 years to over 70 years.[1] Liver disease is commonly the first symptom in children and younger adults and is very rarely accompanied by neurologic or psychiatric symptoms, while neurologic/psychiatric symptoms are usually presenting symptoms in adults and can be present with or without liver findings.[4] Kayser-Fleisher rings, resulting from copper deposition in the cornea, are considered a hallmark finding in patients with Wilson disease and are present in approximately 90%-95% of patients presenting with neurologic or psychiatric symptoms and in over half of those without these symptoms. However, in children presenting with liver disease Kayser-Fleischer rings are usually absent.[2, 3] Liver findings are highly variable ranging from abnormalities on liver function tests to acute liver failure, acute hepatitis or liver cirrhosis.[4] Fatty liver, chronic liver disease and hemolytic anemia may also be present.[3] Neurologic findings include tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis, and spastic dystonia, while psychiatric findings include depression, neurotic behavior, mood disturbance and intellectual deterioration.[3] Other symptoms include renal involvement, arthritis, reduced bone mineral density, pancreatitis, cardiomyopathy, cardiac arrhythmias, rhabdomyolysis, endocrine disorders and sunflower cataracts.[3] If untreated, Wilson disease can be lethal; however, symptoms can be prevented if affected patients are diagnosed and treated early.[5]

Genetics and Biochemical Features:

Wilson disease is caused by pathogenic variants in the *ATP7B* gene that is located on chromosome 13q14 and encodes a copper-transporting P-type ATPase, which delivers copper for incorporation into apoceruloplasmin and excretion into the bile. Impaired ATP7B function results in excessive cellular copper accumulation and clinical symptoms. A diagnosis of Wilson disease is based on a combination of clinical and laboratory findings. Biochemical tests include liver function tests, liver biopsy findings, liver copper concentration, serum ceruloplasmin concentration and 24-hour urinary copper concentration. Ultimately, confirmation of a diagnosis depends on the identification of disease-causing variants.[6] The incidence of Wilson disease is estimated to be 1 in 30,000 individuals although the prevelance has been reported to be higher in certain regions and ethnic groups.[5]

Test Methods:

Variant analysis of the *ATP7B* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-21, and corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing or another appropriate method.

Test Sensitivity:

In a number of studies including large numbers of patients with Wilson disease from different ethnic backrounds, sequencing of the *ATP7B* gene identified reportedly pathogenic variants in 65% to 94% of alleles.[1, 4, 5, 6, 7] In 142 Chinese patients, sequencing plus reflexive multiplex ligation-dependent probe amplification (MLPA) testing, identified disease-causing variants in approximately 98% of alleles.[8]

Variant Spectrum:

At this time there are over 900 variants in the *ATP7B* gene associated with Wilson disease in the Human Gene Mutation Database. The vast majority are missense, with nonsense, splicing, regulatory, small deletions/insertions and large deletions also reported. In 168 Chinease patients, exon-level large deletions of *ATP7B* were identified on 6 alleles.[8] At this time, there is poor genotype-phenotype correlation for Wilson disease.[9] However, individuals homozygous for the p.H1069Q variant, which accounts for 35%-45% of Wilson disease alleles in a mixed European population, have a mean age of onset of 20 to 22 years.[3] Other variants common to specific ethnic groups include p.R778L, accounting for approximately 57% of disease alleles in the Asian population younger than 18 years and a 15 bp deletion in the promotor region which is common in Sardinia.[3]

References:

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