



## ATP7B sequencing for Wilson disease

### Clinical Features:

Wilson disease is characterized by:

- Hepatic symptoms—recurrent jaundice; chronic liver disease; fatty liver; simple, acute, self-limited hepatitis-like illness; autoimmune hepatitis; fulminant hepatic failure; and hemolytic anemia
- Neurologic presentation—movement disorders or spastic dystonia disorders
- Psychiatric disturbances—depression, neurotic behaviors, disorganization of personality, and intellectual deterioration

These manifestations may appear from three to over 50 years of age. Another common finding is Kayser-Fleischer rings (copper deposits in the periphery of the cornea), which are observed in approximately 50-60% of individuals with liver disease and in 90% of individuals with either psychiatric disturbances or neurologic findings (1). Heterozygotes have not been reported to have clinical symptoms.

### Diagnosis:

Biochemical testing can be used to support the diagnosis of Wilson disease. Two of the three following findings is a strong support for a diagnosis:

- Low serum ceruloplasmin concentration. However, at least 5% of individuals with neurologic symptoms and 40% of individuals with hepatic symptoms will have a normal serum ceruloplasmin concentration.
- High urinary copper (above 0.6  $\mu\text{mol}/24$  hours)
- Increased hepatic copper concentration (usually greater than 250 $\mu\text{g}/\text{g}$  dry weight; normal levels are less than 55 $\mu\text{g}/\text{g}$  dry weight).

Heterozygotes might have low serum ceruloplasmin concentration, borderline normal urinary copper, and elevated hepatic copper (100-250 $\mu\text{g}/\text{g}$  dry weight) (1).

### Treatment:

There is effective treatment for Wilson disease, and this makes early diagnosis important to prevent from severe complications. Therapy begins as soon as the individual is diagnosed. The treatment is lifelong, including during pregnancy. Copper chelating agents (penicillamine and trientine), zinc (metallothionein inducer) or antioxidants can be used. Affected individuals are advised to avoid foods with very high copper concentration, such as liver, shellfish, nuts, chocolates, and mushrooms. For individuals that fail to respond to these treatments, liver transplantation might be an option (1, 2).

### Molecular Genetics:

Currently the only gene associated with Wilson disease is *ATP7B* (OMIM # 606882) located at 13q14.3. *ATP7B* codes for a copper-transporting P-type ATPase (3). In Wilson disease, a defect in this enzyme that plays a role in biliary excretion of excess copper causes copper accumulation and toxicity in the body, especially in the liver and brain (4). *ATP7B* has homology to *ATP7A*, which is the gene responsible for Menkes disease. More than 40 normal allelic variants and over 200 mutations have been identified in several ethnic groups. The European population has a common mutation at the ATP-binding region (H1069Q), and the Asian population has a common amino acid substitution in exon 8, R778L (3, 5). While mutations in the promoter region are rare, they predominate in the Sardinian population (6). Complete gene sequencing detects mutations in approximately 98% of individuals with Wilson disease (1).

### Inheritance:

Wilson disease is an autosomal recessive disorder with a prevalence of 1/30,000, and a carrier frequency of 1/90. The prevalence for China, Japan, and Sardinia is higher than the general population (1/10,000). Each sibling of an affected individual has a 25% chance of being affected, 25% chance of being unaffected, and 50% chance of being a carrier.

## Additional Resources:

### Wilson's Disease Association International

Phone: (330) 264-1450

Toll free: (888) 264-1450

Fax: (330) 264-0974

E-mail: [info@wilsonsdisease.org](mailto:info@wilsonsdisease.org)

[www.wilsonsdisease.org](http://www.wilsonsdisease.org)

## Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. We also offer deletion/duplication analysis of the *ATP7B* gene by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing.

### ATP7B sequencing analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81406
Turn-around time:	4 weeks

### ATP7B deletion/duplication analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81405
Turn-around time:	4 weeks

## Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

***For more information about our testing options, please visit our website at [dnatesting.uchicago.edu](http://dnatesting.uchicago.edu) or contact us at 773-834-0555.***

## References:

1. Cox D, Roberts E. Wilson Disease. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 1999.
2. Roberts EA, Schilsky ML, Division of Gastroenterology and Nutrition HfSC, Toronto, Ontario, C.nada. A practice guideline on Wilson disease. *Hepatology* 2003; 37: 1475-1492.
3. Tanzi RE, Petrukhin K, Chernov I et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. *Nat Genet* 1993; 5: 344-350.
4. Brewer GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc Soc Exp Biol Med* 2000; 223: 39-46.
5. Thomas GR, Forbes JR, Roberts EA et al. The Wilson disease gene: spectrum of mutations and their consequences. *Nat Genet* 1995; 9: 210-217.
6. Cullen LM, Prat L, Cox DW. Genetic variation in the promoter and 5' UTR of the copper transporter, ATP7B, in patients with Wilson disease. *Clin Genet* 2003; 64: 429-432.

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