Wilson Disease: \( \text{ATP7B} \) Gene Sequencing

Test Code: SAT7B  
Turnaround time: 6 weeks  
CPT Codes: 81406 x1

**Condition Description**

Wilson disease is a disorder of copper metabolism that can present with hepatic, neurologic, or psychiatric disturbances, or a combination of these, in individuals ranging from age three years to over 50 years. Phenotypic expression varies even within families. The phenotypic spectrum has further expanded through molecular genetic testing, which has confirmed the diagnosis in individuals with atypical clinical and biochemical findings.

Liver disease occurs in approximately 40% of individuals with Wilson disease, usually presenting within ages 6-45 years. The presentation can vary and includes the following findings: recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, or chronic liver disease.

Neurologic presentation occurs in approximately 40% of individuals with Wilson disease, usually presenting within ages 6-50 years. Neurologic involvement follows two general patterns: movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement).

Psychiatric disturbance occurs in approximately 20% of individuals with Wilson disease, usually presenting during adolescence or young adulthood. The psychiatric manifestations are variable and can include depression, neurotic behaviors, disorganization of personality, and, occasionally, intellectual deterioration.

Kayser-Fleischer rings result from copper deposition in Descemet's membrane of the cornea and reflect a high degree of copper storage in the body. These copper deposits in the periphery of the cornea are observed in approximately 50-60% of individuals with liver disease and about 90% of individuals with either neurologic findings or psychiatric disturbance. They are observed most reliably by slit lamp examination. Other findings can include arthritis, pancreatitis, cardiomyopathy, cardiac arrhythmias, rhabdomyolysis, endocrine disorders, and sunflower cataracts.

Diagnosis of Wilson disease depends upon the detection of low serum copper and ceruloplasmin concentrations, increased urinary copper excretion, the presence of Kayser-Fleisher rings in the cornea, and/or increased hepatic copper concentration. \( \text{ATP7B} \) (13q14.3-q21.1) is the only gene known to be associated with Wilson disease. Molecular genetic testing is playing an increasingly important role in diagnosis, as copper studies are frequently equivocal. Complete gene sequencing detects mutations in about 98% of individuals with Wilson disease.

Heterozygotes have not been reported to have clinical symptoms. However, they may have low serum ceruloplasmin concentrations, borderline normal urinary copper, elevated urinary copper on provocative testing with penicillamine, and/or moderate elevation of hepatic copper (100-250 mg/g dry weight). Testing using serum concentrations of copper and ceruloplasmin or provocative testing with penicillamine is not reliable for distinguishing carrier status from either normal or affected. Because of the unreliability of distinguishing heterozygotes from presymptomatic individuals, molecular genetic testing should be used.

Wilson disease is inherited in an autosomal recessive manner. The prevalence of Wilson disease is estimated at one in 30,000 in most populations, with a corresponding carrier frequency in the general population of one in 90. The prevalence is as high as one in 10,000 in China, Japan, and Sardinia.

**References:**

- GeneReviews: Wilson Disease
- OMIM #277900 Wilson Disease

**Genes**

\( \text{ATP7B} \)

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of Wilson disease
- Carrier testing in adults with a family history of Wilson disease

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: Molecular genetic testing identifies mutations in \( \text{ATP7B} \) in approximately 98% of affected individuals. Mutations in the promoter
region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

**Related Tests**

- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.