Wilson disease genetic tests

Clinical Features in Patients with Wilson Disease

Hepatic

- Asymptomatic hepatomegaly
- Isolated splenomegaly
- Persistently elevated serum aminotransferase activity (AST, ALT)
- Fatty liver, Acute hepatitis, Resembling autoimmune hepatitis
- Cirrhosis: compensated or decompensated
- Acute liver failure

Neurological

- Movement disorders (tremor, involuntary movements)
- Drooling, dysarthria, Rigid dystonia
- Pseudobulbar palsy, Dysautonomia, Migraine headaches, Insomnia, Seizures

Psychiatric

- Depression, Neurotic behaviours, Personality changes, Psychosis

Other Systems

- Ocular: Kayser-Fleischer rings, sunflower cataracts
- Cutaneous: lunulae ceruleae · Renal abnormalities: aminoaciduria and nephrolithiasis
- Skeletal abnormalities: premature osteoporosis and arthritis · Cardiomyopathy, dysrhythmias · Pancreatitis · Hypoparathyroidism
- Menstrual irregularities; infertility, repeated miscarriages

How is Wilson disease diagnosed?

The diagnosis of Wilson disease is made by relatively simple tests. The tests can diagnose the disease in both symptomatic patients and people who show no signs of the disease. These tests can include:

- Opthalmalogic slit lamp examination for Kayser-Fleischer rings
- Serum ceruloplasmin test
- 24-hour urine copper test
- Liver biopsy for histology and histochemistry and copper quantification
- Genetic testing, haplotype analysis for siblings and mutation analysis.

It is important to diagnose Wilson disease as early as possible, since severe liver damage can occur before there are any signs of the disease. Individuals with Wilson disease may falsely appear to be in excellent health.

Treatment of Wilson disease

Wilson disease is a very treatable condition. With proper therapy, disease progress can be halted and oftentimes symptoms can be improved. Treatment is aimed at removing excess accumulated copper and preventing its reaccumulation. Treatment for Wilson disease is a lifelong process. Patients may become progressively sicker from day to day, so immediate treatment can be critical. Treatment delays may cause irreversible damage.

Chelation therapy drugs approved for treating Wilson disease include penicillamine(Cuprimine® and Depen®)and trientine (Syprine® and Trientine Dihydrochloride) Both of these drugs act by chelation or binding of copper, causing its increased urinary excretion.

Mettalothionein inducer drugs approved for treating Wilson disease are (Galzin™) in the U. S. and (Wilzin®)in Europe. Zinc acts by blocking the absorption of copper in the intestinal tract. This action both depletes accumulated copper and prevents its reaccumulation. Zinc’s effectiveness has been shown by more than 30 years of considerable experience overseas. A major advantage of zinc therapy is its lack of side effects.

Patients with severe hepatitis or liver failure may require liver transplant. Patients being investigated or treated for Wilson disease should be cared for by specialists in Wilson disease or by specialists in consultation with their primary physicians. Stopping treatment completely will result in death, sometimes as quickly as within three months. Decreasing dosage of medications also can result in unnecessary disease progression.

How is Wilson disease inherited?

Wilson disease is an autosomal recessive disease, which means it occurs equally in men and women. In order to inherit Wilson disease, both parents must carry one genetic mutation (abnormal alteration in the gene) that each parent passes to the affected child. At least one in 30, 000 people of all known races and nationalities has the disease. Of the 23 different human chromosomes, the gene responsible for Wilson disease is located on chromosome 13. The gene is called ATP7B and it contains the genetic information necessary to make a copper transport protein that plays a key role in incorporating copper into ceruloplasmin and moving excess copper out of the liver. Mutations in the gene lead to an abnormal copper transporter that cannot move copper effectively or at all. More than 300 genes of the ATB7B have been identified thus far. This excess copper

accumulates in the liver and other organs. Most patients have no family history of Wilson disease. People with only one abnormal gene are called carriers. Carriers (heterozygotes) may have mild, but medically insignificant, abnormalities of copper metabolism. Carriers do not become ill and should not be treated. Wilson disease patients (homozygotes) do become ill and must receive treatment lifelong or eventually they will develop severe lethal disease.

One in 100 individuals in the general population carries one abnormal copy of the Wilson disease gene. Carriers have one normal and one abnormal gene. All (100%) children of those afflicted with Wilson disease receive at least one abnormal copy of the Wilson disease gene. One half (50%) of a carrier's children receive at least one abnormal copy of the Wilson disease gene. A genetic counselor can provide a more detailed pedigree of specific family relationships.

Family Screening

All siblings and children of Wilson disease patients should be tested for Wilson disease. Other relatives who have had symptoms or laboratory tests that indicate liver or neurological disease also should be tested for Wilson disease. Biochemical Testing Children of patient: Begin at age 2 if asymptomatic, repeat once in 5 years unless reasontopursue further.

Siblings of patient:

- Physical examination and brief history of any liver or neurological symptoms.
- Liver Function Tests: ALT, AST, Albumin, Bilirubin.

- Ceruloplasmin and Serum Copper.
- 24 hour urine copper
- Slit-lamp exam of the eyes for Kayser-Fleischer rings.
- If no K-F rings, abnormal liver functions tests, and low ceruloplasmin: liver bio

Information about Molecular Genetic Testing

All siblings and children of Wilson disease patients should be tested for Wilson disease. Other relatives who have had symptoms or laboratory tests that indicate liver or neurological disease also should be tested for Wilson disease. More than 300 different mutations of the ATP7B gene have been identified thus far.

Testing Methods Available:

Linkage analysis (Haplotype analysis) Molecular genetic testing to identify a set of closely linked segments of DNA (a marker or set of markers), comparing the markers of family members to those of an affected patient.

Useful for: screening siblings of an identified patient Gene sequencing (mutation screening of the entire ATP7B gene) Analysis of the entire ATP7B gene to detect and identify disease causing mutations. An individual with confirmed Wilson disease needs to be tested first. If both mutations are identified, other family members can then be offered testing. Gene sequencing will identify both mutations in most but not all cases of Wilson disease.

Useful for: confirmation of the diagnosis in suspected patients, family members to learn if they could be affected but do not yet have symptoms, to learn they are carriers, or to allow for prenatal testing for confirmed carriers.

Analysis of a specific location in the ATP7B gene for a known particular mutation.

Useful for: specific populations of patients where the common mutations are known; for screening siblings of patients with two identified mutations. Genetic testing is best coordinated through a genetic counselor who can carefully discuss the best method of testing to perform and the benefits, limitations, and implications of each method. Genetic testing is best coordinated though a genetic counselor who can carefully discuss the best method of testing to perform and the benefits, limitations, and implications of each method. Your physician should be able to direct you to a qualified genetic counselor and genetic testing facility.

Definition: Kayser-Fleischer Ring: Clinical sign. Brownish-yellow ring visible around the corneo-scleral junction (limbus). Consists of copper deposits in Descemet’s membrane, extending into the trabecular meshwork. Sign of Wilson’s disease.

Description and Location: Golden to greenish-brown annular deposition of copper located in the periphery (limbus) of the cornea (Descemet’s membrane). First appears as a superior crescent, then develops inferiorly and ultimately becomes circumferential. Usually requires a slit-lamp examination to detect rings in their early stage of formation.

Prevalence: Approximately 95% of WD patients presenting with neurological signs will have a K-F ring. Whereas approximately 65% of WD patients presenting with hepatic signs will present with a ring.

Copper chelation therapy may cause fading and even disappearance of the corneal copper over time.