GENEReviews

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Wilson Disease

[*Hepatolenticular Degeneration*]

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Summary

Disease characteristics. 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; symptoms vary among and within families. **Liver disease** includes recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, or chronic liver disease. **Neurologic presentations** include 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** includes 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.

Diagnosis/testing. 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. *ATP7B* is the only gene known to be associated with Wilson disease. Molecular genetic testing of the *ATP7B* gene is clinically available. The mutation detection rate varies depending on the test method and the individual's ethnicity. Molecular genetic testing is playing an increasingly important role in diagnosis, as copper studies are frequently equivocal. Molecular genetic testing is important for determining the genetic status of at-risk sibs.

Management. Treatment of individuals with Wilson disease by copper chelating agents or zinc can prevent the development of hepatic, neurologic, and psychiatric findings in asymptomatic affected individuals and can reduce findings in many symptomatic individuals. Lifelong treatment with chelating agents is initiated as soon as possible in individuals with symptomatic Wilson disease. Copper chelating agents (penicillamine or trientine) increase urinary excretion of copper. High-dose oral zinc interferes with absorption of copper from the gastrointestinal tract and is most effective after initial decoppering with a chelating agent.

Antioxidants, such as vitamin E, may be used with a chelator or zinc to prevent tissue damage, particularly to the liver. Foods high in copper are restricted, especially at the beginning of treatment. Orthotopic liver transplantation is used for individuals who fail to respond to medical therapy or cannot tolerate it. Molecular genetic testing of sibs of a proband with Wilson disease ensures that therapies are initiated before symptoms occur.

Genetic counseling. Wilson disease is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Prenatal testing for pregnancies of couples who have a child affected with Wilson disease is possible when the disease-causing mutations have been identified in the affected family member or if linkage has been established in the family.

Diagnosis

Clinical Diagnosis

The diagnosis of Wilson disease is suspected in individuals from age three to 60 years (commonly 6-45 years), with varying combinations of hepatic, neurologic, and psychiatric disturbances.

Kayser-Fleischer rings. 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.

Testing

Biochemical testing used in support of the diagnosis of Wilson disease. The biochemical diagnosis in a symptomatic individual relies upon demonstration of abnormal copper parameters. A combination of any two of the following three findings (1-3) is strong support for a diagnosis of Wilson disease.

1 **Low serum ceruloplasmin concentration**

- **In children,** interpretation of test results requires age correction or age-specific reference ranges.

  Note: Healthy newborns have low serum ceruloplasmin concentrations. The concentrations increase during the first six months of life and by two to three years of age peak at a concentration that may exceed the healthy adult reference range.

- **In adults** with Wilson disease, serum ceruloplasmin concentration is often below the normal range and typically very low.

  Note: A normal serum ceruloplasmin concentration is found in at least 5% of individuals with Wilson disease with neurologic symptoms and up to 40% of individuals with hepatic symptoms [Steindl et al 1997]. Serum ceruloplasmin concentration is, therefore, not a reliable screening test for Wilson disease.

2 **High urinary copper.** Measurement of copper in three 24-hour urine collections, free from contamination by external sources of copper, is advised. The testing

laboratory should be consulted regarding its trace-element urine collection protocol prior to initiating urine specimen collection.

- **Basal urinary copper excretion** (without the use of chelating agent) is almost invariably elevated above 0.6 µmol/24 hours in the symptomatic individual.
- **A provocative test of urinary copper excretion** following oral administration of penicillamine is useful in many cases [Martins da Costa et al 1992], although levels in affected individuals can overlap with those of heterozygotes.

3 **Increased hepatic copper concentration.** Hepatic copper concentration in Wilson disease is usually greater than 250 µg/g dry weight (normal: <55 µg/g dry weight [Nuttall et al 2003]); however, such levels may be seen in other chronic liver disorders as well.

Note: (1) In later stages of Wilson disease, copper is distributed unevenly in the liver and measurement of hepatic copper concentration is less reliable. (2) Some individuals have only a moderately elevated hepatic copper concentration — 100 to 250 µg/g dry weight, which overlaps with values occasionally found in heterozygotes. Thus, hepatic copper concentration in this range does not exclude the diagnosis of Wilson disease.

Biochemical testing that cannot consistently support the diagnosis of Wilson disease

- **High non-ceruloplasmin-bound serum copper concentration** often present as a result of copper overlaod, is not always reliable for diagnosis because of its high dependency on the accuracy of both serum ceruloplasmin and serum copper concentration.
- **Serum concentration of copper** is low in healthy newborns. The concentrations increase during the first six months of life and by two to three years of age peak at a concentration that may exceed the healthy adult reference range.

  Most adults with Wilson disease have a subnormal serum copper concentration that is proportional to the serum ceruloplasmin concentration. The combination of low ceruloplasmin serum concentration and a normal or high serum copper concentration suggests excess non-ceruloplasmin-bound copper in the serum.
- **The serum concentration of non-ceruloplasmin-bound copper** (in µg/L) is most reliably estimated by subtracting the amount of copper associated with ceruloplasmin, determined by the enzymatic assay (ceruloplasmin in mg/L x 3.15) from the total serum copper concentration. Normal serum concentration of non-ceruloplasmin-bound copper is approximately 50-100 µ/L. In individuals with Wilson disease, the serum concentration of non-ceruloplasmin-bound copper is usually higher than 200 µ/L.

  Note: Enzymatic methods for quantification of ceruloplasmin measure holoceruloplasmin (i.e., with copper incorporated) and are therefore preferred, particularly for calculation of free copper concentration [Walshe 2003a, Macintyre et al 2004].

Biochemical testing that is not used in the diagnosis of Wilson disease

- **Incorporation of copper into ceruloplasmin.** In individuals with Wilson disease, incorporation of copper into ceruloplasmin is impaired following oral or intravenous administration of a radio-labeled or stable isotope of copper. This test is rarely available and has limited utility now that molecular testing is available.

Heterozygotes. 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). A secure diagnosis is essential in such individuals to avoid inappropriate lifelong therapy for heterozygotes.

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.

Molecular Genetic Testing

Molecular Genetic Testing —Gene. *ATP7B*, encoding a copper-transporting P-type ATPase, is the only gene currently known to be associated with Wilson disease.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** Some of the more common mutations found in the *ATP7B* gene:
  - **H1069Q** [Tanzi et al 1993] is the only mutation found relatively frequently in populations of European origin. It accounts for 35-45% of Wilson disease alleles in a mixed European population and a greater percent in eastern Europe [Caca et al 2001]. The frequency of this mutation may be somewhat lower in probands with childhood onset and in probands presenting with liver disease.
  - **R778L** [Thomas et al 1995] is the only relatively common mutation in Asian populations, accounting for approximately 57% of Wilson disease alleles in the Asian population younger than 18 years of age.

    A single mutation, 15-bp deletion, has been identified in the 1-kb promoter, non-coding region and is common in Sardinia [Loudianos et al 1999]. Promoter mutations have not been described in other populations and are presumed to be rare [Cullen et al 2003].
  - **Panels** to detect a limited number of mutations appear to be feasible in selected populations, such as those in Sardinia [Lovicu et al 2003] and Eastern Germany [Huster et al 2004].

Note: The detection rate of targeted mutation analysis varies depending on the mutations included in the testing panel and the ethnicity of the individual.

- **Sequence analysis, HPLC, or SSCP mutation scanning of selected exons.** The mutation detection rate varies depending on the regions analyzed and the ethnicity of the individual.
  - **Mutations in exons 8, 14, and 18.** account for approximately 60% of alleles in the British population [Curtis et al 1999].
  - **Exons 8 and 12.** Mutations in exons 8 and 12 account for approximately 57% of alleles in the Chinese population [Wu et al 2001].
- **Sequence analysis of coding region.** Complete gene sequencing detects mutations in about 98% of individuals with Wilson disease [DW Cox, unpublished].
- **Deletion/duplication testing.** Large deletions and duplications, encompassing one or more exons, are rare, unlike the situation in the related *ATP7A* gene defective in Menkes disease. A deletion of exons 20 and 21 has been reported [Moller et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Wilson Disease

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	*ATP7B* mutation panel varies by laboratory	Depends on the mutations included in the panel and individual's ethnicity	Clinical Testing
Sequence analysis/mutation scanning of select exons	*ATP7B* sequence variants	Depends on exons analyzed, individual's ethnicity, and method used	
Sequence analysis of coding region		About 98%	
Deletion/duplication testing	*ATP7B* large duplications, deletions	Unknown	

Interpretation of test results

- An evaluation of missense mutations is provided in the Wilson Disease Mutation Database. Missense mutations comprise over 50% of those listed. The functional status of some 12% of the missense mutations listed remains in question.
- Not all splice site mutations have been proven to affect splicing. Only about 17% have been tested.
- For many of the mutations, controls of the same ethnic origin have not been analyzed. Care must therefore be taken in interpreting the mutation results.
- The identification of only one of the two disease-causing mutations may be adequate to confirm a diagnosis in the presence of definite clinical symptoms and typical abnormal biochemical tests. However, the one mutation identified must clearly be a disease-causing mutation, and not a missense mutation that could be a rare normal variant. If questions remain regarding the significance of the mutation, the second mutation should be identified.

Linkage analysis. For individuals and families for whom neither or only one mutation is known, linkage analysis is useful for early diagnosis of at-risk sibs, prenatal diagnosis, and carrier detection. The accuracy of linkage analysis is dependent on: (1) accurate clinical diagnosis of Wilson disease in the affected family member(s); and (2) informative genetic markers, flanking with the *ATP7B* gene, within the family. Samples from parents and sibs (including a sample from at least one affected individual) are necessary to perform linkage analysis. The microsatellite markers flanking the gene (e.g., D13S316, D13S301, and D13S314) are informative in approximately 90% of families [Cox 1996]. Flanking markers on

both sides of the gene must be unambiguously informative to avoid an error resulting from undetected recombination.

Testing Strategy for a Proband

1. The diagnosis is often established by biochemical testing.
2. In individuals in whom the diagnosis is not clearly established biochemically and clinically, molecular genetic testing is useful to identify the two disease-causing alleles, or in some cases one allele.

Note: A diagnostic index, based on clinical, biochemical, and molecular features, has been proposed but has not been validated in large patient series [Ferenci et al 2003].

Genetically Related Disorders

No other phenotypes are currently known to be associated with mutations in the *ATP7B* gene.

MURR1(COMMD1) is a candidate gene for causing recessive copper toxicosis in Bedlington terriers [van de Sluis et al 2002, Coronado et al 2003] but has not been shown to be involved in early childhood copper toxicosis [Muller et al 2003] or in other copper storage disorders suggestive of Wilson disease [Coronado et al 2005].

Clinical Description

Natural History

Wilson disease can present with hepatic, neurologic, hematologic, or psychiatric disturbances, or a combination of these, in individuals ranging in age from three years to over 50 years [Walshe 1989, Dening & Berrios 1989, Steindl et al 1997, Cox & Roberts 2005]. 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.

Table 2 outlines the typical presentations of Wilson disease. Of note, the "classic triad" of liver disease, movement disorder, and Kayser-Fleischer ring is uncommon.

Table 2. Clinical Findings in Individuals with Wilson Disease by Presenting Finding

Presenting Finding	% of Individuals	Typical Age of Presentation (Range)	Liver Disease	Neurologic Disease	Psychiatric Disturbance	Kayser-Fleischer Rings
Liver disease	~40%	6-45 (3-70)	+	+/–	+/–	~50%
Neurologic disease	~40%	Mid-teen - mid-adult (6-50)	–/Mild	+	+/–	~90%
Psychiatric disturbance	~20%	Adolescent - young adult	–/Mild	+/–	+	~90%
Hemolitic anemia	Few %	Adolescent - young adult	+	–	–	+

Liver disease. Wilson disease presents with liver disease more commonly in children and younger adults, typically between the ages of six and 45 years; however, severe liver disease can be a presenting finding in preschool-aged children [Wilson et al 2000] and in older adults. The presentation can vary and includes the following findings:

- **Recurrent jaundice,** possibly caused by hemolysis

- **Simple, acute, self-limited hepatitis-like illness** with fatigue, anorexia, abdominal pain
- **Autoimmune hepatitis,** often presenting acutely with fatigue, malaise, arthropathy, and rashes. This form of liver disease responds well to chelation therapy even if cirrhosis is present (see Management).
- **Fulminant hepatic failure** with severe coagulopathy, encephalopathy, acute Coombs-negative intravascular hemolysis, and often rapidly progressive renal failure. Serum activity of aminotransferases is only moderately increased, and serum concentration of alkaline phosphatase is normal or extremely low. These individuals do not respond to chelation treatment and require urgent liver transplantation (see Management).
- **Chronic liver disease** with portal hypertension, hepatosplenomegaly, ascites, low serum albumin concentration, and coagulopathy
- **Fatty liver** of mild to moderate degree with abnormal liver function
- **Hemolytic anemia, with either acute or chronic hemolysis,** is a reflection of a high serum concentration of non-ceruloplasmin-bound copper, which leads to destruction of erythrocytes. Liver disease is likely to be present in such cases, as are Kayser-Fleischer rings. Recurrent hemolysis predisposes to cholelithiasis, even in children.

Neurologic presentation. Neurologic involvement follows two general patterns: movement disorders or rigid dystonia.

- Movement disorders tend to occur earlier and include tremors, poor coordination, loss of fine-motor control, micrographia, chorea, or choreoathetosis.
- Spastic dystonia disorders present with mask-like facies, rigidity, and gait disturbance [Svetel et al 2001].

Pseudobulbar involvement such as dysarthria, drooling, and difficulty swallowing is more common in older individuals, but also occurs in children and adolescents.

In contrast to the individuals with a frank neurologic presentation, the neurologic findings in individuals with a hepatic presentation are mood disturbance (mainly depression; occasionally poor impulse control), changes in school performance, and/or difficulty with fine motor skills (especially handwriting) or gross motor skills.

Psychiatric disturbance. The psychiatric manifestations are variable. Depression is common. Neurotic behavior includes phobias, compulsive behaviors, aggression, or antisocial behavior. Older individuals may have subtle psychopathology such as progressive disorganization of personality with anxiety and affective changes such as labile mood and disinhibition. Intellectual deterioration may also occur with poor memory, difficulty in abstract thinking, and shortened attention span. Pure psychotic disorders are uncommon.

Kayser-Fleischer rings. These result from copper deposition in Descemet's membrane of the cornea, and reflect a high degree of copper storage in the body. They are reduced or disappear with effective treatment.

Other findings

- Renal involvement. Low-molecular weight proteinuria, microscopic hematuria, and Fanconi syndrome
- Arthritis. Involvement of large joints from synovial copper accumulation

- Pancreatitis, cardiomyopathy, cardiac arrhythmias, rhabdomyolysis of skeletal muscle, and various endocrine disorders
- Sunflower cataracts. Observed occasionally on slit lamp examination
- Hepatocellular carcinoma rarely develops in Wilson disease, but abdominal malignancies have been reported in treated individuals [Walshe et al 2003].

Fertility and pregnancy. Most individuals with Wilson disease are fertile. Successful pregnancies of women with Wilson disease who received treatment have been reported [Tarnacka et al 2000, Furman et al 2001]. Prior to diagnosis and treatment, affected women may experience infertility or recurrent miscarriage.

Genotype-Phenotype Correlations

Mutations that completely prevent function of the gene tend to produce a more severe phenotype than certain types of missense mutation [Cox 1996,Liu et al 2004,Deguti et al 2004]. In general, the most severe mutations result in onset of symptoms before age 12 years, frequently with liver manifestations [Panagiotakaki et al 2004]. Mutations in transmembrane domain 4 can be associated with severe manifestations [Wu et al 2001]. However, disease severity and clinical features are also influenced by other modifying factors, as suggested by marked differences between sibs in some families.

Several studies have found a mean age of onset of 20 to 22 years in individuals homozygous for the common H1059Q mutation [Stapelbroek et al 2004], although earlier onset also occurs.

Heterozygotes are not known to develop clinical manifestations of Wilson disease.

Nomenclature

The neurologic form of Wilson disease has also been known as Westphal-Strumpell pseudosclerosis.

Prevalence

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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Other liver diseases presenting with abnormal liver biochemistries with or without hepatomegaly that need to be considered:

- Chronic viral hepatitis
- Autoimmune hepatitis
- Primary sclerosing cholangitis
- Drug hepatotoxicity
- HFE-associated hereditary hemochromatosis
- Alpha-1-antitrypsin deficiency
- Non-alcoholic steatohepatitis (NASH) *

- Alcoholic liver disease
- Primary biliary cirrhosis

* Note: Wilson disease must be specifically excluded in individuals thought to have NASH or the opportunity for life-saving treatment will be missed.

Other liver diseases presenting as fulminant hepatic failure that need to be considered are acute viral hepatitis of any etiology and severe drug toxicity.

Kayser-Fleischer rings are not specific for Wilson disease and may be seen in copper accumulation associated with cholestatic liver diseases or autoimmune hepatitis.

A subnormal serum concentration of ceruloplasmin is not specific for Wilson disease, as ceruloplasmin synthesis can be reduced with acute liver failure or decompensated cirrhosis of any etiology. Serum concentration of ceruloplasmin is physiologically low in neonates. Decreased serum concentrations of ceruloplasmin are observed in protein-losing enteropathy, nephrotic syndrome, malnutrition, but also in some heterozygotes for Wilson disease. Almost complete absence of ceruloplasmin is found in hereditary aceruloplasminemia, which results in iron storage [Miyajima et al 1987, Yoshida et al 1995].

Rare familial/environmental copper storage diseases not related to Wilson disease have been identified; the most common of these is Indian childhood cirrhosis.

Other neurologic disorders that need to be considered:

- Benign familial or essential tremors
- Parkinson disease and its differential diagnoses, including:
  - Huntington disease
  - Dentatorubro-pallidoluysian atrophy (DRPLA)
  - Juvenile Parkinson disease, including Parkin type of juvenile parkinsonism
- Inherited forms of dystonia, including:
  - Early-onset primary dystonia (DYT1)
  - Dopa-responsive dystonia (DRD). See also Dystonia Overview.
- Neurodegenerative diseases
- Drug effects or toxicity
- Hyperthyroidism
- Central nervous system neoplasia
- Hereditary ataxias
- Niemann-Pick disease type C (associated with liver disease)

Management

Treatment of Manifestations

The goal of therapy is to institute treatment with chelating agents as soon as possible in individuals with symptomatic Wilson disease. (See extensive review, American Association for the Study of Liver Diseases Practice Guideline [Roberts & Schilsky 2003].)

- Treatment is lifelong, including during pregnancy.

- If one treatment modality is discontinued, an alternative modality must be substituted.
- Discontinuation of all treatment leads to hepatic decompensation, which is usually refractory to further medical intervention.

Copper chelating agents that increase urinary excretion of copper are the first-line treatment for Wilson disease. Routine institution of chelation therapy before the age of three years has not been adequately assessed and may have adverse effects on growth.

- **Penicillamine (chelator).** Used since the 1950s as first-line therapy for Wilson disease [Durand et al 2001, Walshe 2003b], penicillamine is given as D-penicillamine tablets by mouth two or three times daily. Pyridoxine must be given along with penicillamine. Twenty-four-hour urine copper excretion is used to confirm chelation and increased excretion of copper. Urinary copper values should be five to ten times normal; if the values are lower, non-compliance may be an issue, or body copper stores may have been adequately depleted.

  (1) Complete blood count and urinalysis must be monitored regularly during penicillamine therapy. Serious side effects can occur in up to 30% of individuals, and include: severe thrombocytopenia, leukopenia, aplastic anemia, proteinuria, nephrotic syndrome, polyserositis, Goodpasture syndrome, and severe skin reactions. An early allergic reaction with fever, rash, and proteinuria may occur. The presence of any such side effects requires discontinuation of penicillamine and substitution of an alternate treatment.

  (2) Penicillamine inhibits collagen cross-linking and has some immunosuppressant properties. After decades of treatment, individuals may have abnormal skin and connective tissue collagen; chronic depletion of copper and possibly other trace metals may occur.

  (3) Penicillamine should NOT be used simultaneously with zinc, pending adequate clinical assessment of this treatment strategy.

- **Trientine (chelator),** also known as triethylene tetramine dihydrochloride (2,2,2-tetramine) or trien, is the usual second-line treatment for individuals who cannot tolerate penicillamine. It is gaining acceptance as a first-line drug because of good efficiency and excellent tolerance; however, it is not generally available in all countries.

  Note: (1) Complete blood count and urinalysis must be monitored regularly in all individuals on trientine; (2) rare side effects are gastritis with nausea and iron deficiency anemia; (3) trientine should NOT be used simultaneously with zinc pending adequate assessment of this combination. Current reports suggest that the combination of trientine and zinc, temporally dispersed throughout the day such that each drug is administered 5-6 hours apart from the other, may be effective in severely decompensated hepatic Wilson disease [Santos Silva 1996, Askari et al 2003].

Zinc (metallothionein inducer). High-dose oral zinc interferes with absorption of copper from the gastrointestinal tract by inducing enterocyte metallothionein, which preferentially binds copper from the intestinal contents and is lost in the feces as enterocytes are shed in normal turnover. Zinc therapy is most effective after initial decoppering with a chelating agent [Brewer 2001, Brewer et al 2001]. In selected cases, it can be used as an initial treatment [Milanino et al 1992]. Zinc is taken as tablets by mouth at least twice (usually three times)

daily, before meals. The dose is based on the elemental zinc in the tablet. Twenty-four-hour urine copper excretion is used to monitor total body copper stores, which should decrease. The computed estimate of non-ceruloplasmin-bound copper may be used to titrate the zinc dose. Serum or urinary zinc concentration can be measured to monitor compliance in individuals taking zinc.

Note: (1) Gastritis, a common side effect, can be reduced with the use of zinc acetate or zinc gluconate; (2) zinc should NOT be used simultaneously with any chelator, pending further clinical investigation.

Antioxidants. Serum and hepatic vitamin E concentrations are reported to be low in individuals with Wilson disease [Sokol et al 1994, Ogihara et al 1995], likely because of excessive consumption to counteract free radicals produced by excess copper. Antioxidants, such as vitamin E, may be used along with a chelator or zinc in protecting tissues from damage.

Restriction of foods very high in copper (liver, brain, chocolate, mushrooms, shellfish, nuts) seems prudent, especially at the beginning of treatment. It is recommended that individuals with special dietary needs (e.g., vegetarians) consult with a trained dietitian.

Orthotopic liver transplantation (OLT) is reserved for individuals who fail to respond to medical therapy or cannot tolerate it because of serious adverse side effects [Schilsky et al 1994, Emre et al 2001, Sutclilffe et al 2003]. It remains controversial whether orthotopic liver transplantation should be a primary treatment for individuals with Wilson disease who have severe neurologic disease.

Agents/Circumstances to Avoid

- Foods very high in copper (liver, brain, chocolate, mushrooms, shellfish, nuts), especially at the beginning of treatment

Testing of Relatives at Risk

The goal is to identify those sibs of a proband who have Wilson disease preferably before symptoms occur so that the therapies described under Treatment of Manifestations can be initiated as soon as possible.

- Because presymptomatic individuals generally have a low serum concentration of ceruloplasmin and mildly increased basal 24-hour urinary copper excretion, biochemical testing can be used for their detection, but it is important to note that asymptomatic affected individuals cannot be distinguished from heterozygotes in some cases.
- Affected sibs can be identified more reliably by molecular genetic testing, either by mutation analysis (if both disease-causing mutations in the proband are known) or by use of linkage analysis (when markers are fully informative).

Therapies Under Investigation

Ammonium tetrathiomolybdate (chelator) interferes with copper absorption from the intestine and binds plasma copper with high affinity. It may be useful for treatment of severe neurologic Wilson disease because, unlike penicillamine, it appears not to be associated with early neurologic deterioration [Brewer et al 2003]. The safety and efficacy of this drug for treatment of Wilson disease are not established; serious side effects such as bone marrow depression (leukopenia) and hepatitis are problematic. Treatment duration with ammonium tetrathiomolybdate should be limited to only a few months, as copper depletion can occur.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Pregnancy. Treatment must be continued during pregnancy because of the risk of fulminant hepatic failure.

- Penicillamine has been used in many pregnancies with no adverse outcomes, but embryopathy may occur, possibly in about 5% of births. Such adverse outcomes may depend upon dose, which should be kept as low as possible. The dose of penicillamine should be maintained at the lowest effective dose with the plan to reduce by approximately 30% in the third trimester if the mother has been well chelated prior to pregnancy. A possible over-chelated (copper deficiency) status prior to pregnancy or genetic characteristics of the mother can contribute to fetal abnormalities [Pinter et al 2004].
- Trientine has been used successfully during pregnancy, but the total number of reported cases is small.
- Zinc has been used effectively during pregnancy.

Copper deficiency from excessive long-term treatment could result in copper deficiency, leading to immobilization of iron, as observed in aceruloplasminemia. Further studies are required.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Wilson disease is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an individual with Wilson disease are obligate heterozygotes as they carry one mutant allele.
- Clinical disease is not known to occur in carriers although the possibility has not been adequately excluded at older ages.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) with clinical symptoms have not been reported.

Offspring of a proband

- Offspring of an affected individual are obligate carriers.
- Given the carrier rate of one in 90 in the general population, the likelihood that an affected individual would have an affected child is one in 180.
- Because the risk for an affected individual of having an affected child is low, testing of serum ceruloplasmin concentration after one year of age should be an adequate screening in young children with a parent with Wilson disease, except in populations with a high incidence of Wilson disease or a high incidence of consanguinity, in which molecular testing may be useful.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

- Carrier testing is not usually of clinical importance, except in cases of consanguinity or in populations with a high disease prevalence.
- Discrimination of heterozygotes from asymptomatic affected individuals insures that only affected individuals and not heterozygotes are treated.
- Carrier testing is available on a clinical basis if the *ATP7B* disease-causing mutation (s) have been identified in the proband.
- Carrier testing of at-risk family members is available for at-risk relatives in families in which linkage has been informative.
- Testing using serum concentration of copper and ceruloplasmin or provocative testing with penicillamine is not reliable to determine carrier status.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

Predictive testing of adults and children. Because Wilson disease is a treatable condition, it is appropriate to offer predictive testing to asymptomatic at-risk adults and children.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation,

or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Other issues to consider. Prenatal diagnosis of a treatable condition with a good prognosis with early treatment may be controversial if the testing is being considered for the purpose of pregnancy termination. In Wilson disease, diagnosis before early childhood is not necessary for treatment purposes. Although most centers would consider prenatal testing for Wilson disease to be the choice of the parents, careful discussion and examination of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. However, because treatment for Wilson disease is available, requests for PGD for Wilson disease will likely be very uncommon. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Wilson Disease

Gene Symbol	Chromosomal Locus	Protein Name
ATP7B	13q14.3-q21.1	Copper-transporting ATPase 2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Wilson Disease

277900	WILSON DISEASE
606882	ATPase, Cu(2+)-TRANSPORTING, BETA POLYPEPTIDE; ATP7B

Table C. Genomic Databases for Wilson Disease

Gene Symbol	Locus Specific	Entrez Gene	HGMD
ATP7B	ATP7B	540 (MIM No. 606882)	ATP7B

For a description of the genomic databases listed, click here.

Normal allelic variants: More than 40 normal allelic variants have been reported in several ethnic groups. In some studies, normal variants may have been reported as disease mutations.

Pathologic allelic variants: More than 260 mutations in the *ATP7B* gene have been identified in hundreds of affected individuals of different racial groups.

- The most common mutation in populations of European origin is an amino acid substitution in a highly conserved motif close to the ATP-binding region (H1069Q) [Tanzi et al 1993]. This mutation occurs at a frequency of 26-70% in various populations and is associated with neurologic or hepatic disease and a mean onset age of about 20 years [Houwen et al 1995, Thomas et al 1995, Maier-Dobersberger et al 1997, Shah et al 1997].

- The most common mutation in the Asian population is an amino acid substitution in exon 8, R778L [Thomas et al 1995], found at a high frequency in all Chinese [Gu et al 2003] and ethnically related populations studied.
- Mutations in the promoter region are rare [Cullen et al 2003], except in Sardinia where a deletion in the promoter predominates [Loudianos et al 1999].
- The spectrum of mutations differs from that found in *ATP7A* in Menkes disease. Large gene deletions, found in 20% of persons with Menkes disease, are rare in *ATP7B* in Wilson disease.

Normal gene product: The product of the *ATP7B* gene is copper-transporting ATPase 2. The *ATP7B* gene has 57% identity to the gene *(fATP7A*) defective in Menkes disease [Bull et al 1993, Tanzi et al 1993]. The protein is an intracellular transmembrane copper transporter that plays key roles in incorporating copper into ceruloplasmin and in moving copper out of the hepatocyte into bile. The protein is a P-type ATPase, characterized by cation channel and phosphorylation domains containing a highly conserved Asp-Lys-Thr-Gly-Thr (DKTGT) motif, in which the aspartate residue forms a phosphorylated intermediate during the transport cycle. The six copper-binding domains are similar to those found in yeast and bacteria. Eight hydrophobic regions span the cell membrane. Protein structure has been modeled based on a similar calcium transporting ATPase, SERVA1 [Fatemi et al 2002, Morgan et al 2004]. The gene is expressed mainly in liver and kidney.

Abnormal gene product: Tissue damage occurs after excessive copper accumulation resulting from lack of copper transport from the liver. Even when no transporter function is present, accumulation of copper occurs over several years.

A normal variant of *MURR1(COMMD1*) has been proposed to modify the clinical phenotype of Wilson disease [Stuehler et al 2004].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Medline Plus
Wilson's disease

National Center for the Study of Wilson's Disease
432 West 58th St, Suite 614
New York, NY 10019
Phone: 212-523-8717
Fax: 212-523-8708

National Library of Medicine Genetics Home Reference
Wilson Disease

NCBI Genes and Disease
Wilson's disease

American Liver Foundation
75 Maiden Lane, Suite 603

New York, NY 10038
Phone: 800-GO-LIVER (800-465-4837)
Fax: 212-483-8179
Email: info@liverfoundation.org
liverfoundation.org

Canadian Liver Foundation
2235 Sheppard Avenue East, Suite 1500
Toronto, ON
Canada M2J 5B5
Phone: 800-563-5483; 416-491-3353
Fax: 416-491-4952
Email: clf@liver.ca
www.liver.ca

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York, NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

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