



Wilson Disease

Synonym: Hepatolenticular Degeneration

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Created: October 22, 1999; Updated: January 12, 2023.

Summary

Clinical characteristics

Wilson disease is a disorder of copper metabolism that, when untreated, can present with hepatic, neurologic, or psychiatric disturbances – or a combination of these – in individuals ages three years to older than 70 years. Manifestations in untreated individuals vary among and within families.

- Liver disease can include recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, or chronic liver disease.
- Neurologic presentations can include dysarthria, movement disorders (tremors, involuntary movements, chorea, choreoathetosis), dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement), dysautonomia, seizures, sleep disorders, or insomnia.
- Psychiatric disturbances can include depression, bipolar disorder / bipolar spectrum disorder, neurotic behaviors, personality changes, or psychosis.
- Other multisystem involvement can include the eye (Kayser-Fleischer rings), hemolytic anemia, the kidneys, the endocrine glands, and the heart.

Diagnosis/testing

The diagnosis of Wilson disease is established in most instances by a combination of biochemical findings (low serum ceruloplasmin concentration, low serum concentration of total copper, and increased urinary copper excretion) and/or detection of biallelic pathogenic (or likely pathogenic) variants in *ATP7B* identified by molecular genetic testing, based on the diagnostic scoring system developed at the 8th International Meeting on Wilson Disease.

Management

Treatment of manifestations: Lifelong medical interventions to prevent/treat copper accumulation need to be instituted as soon as possible in all individuals with Wilson disease whether they are asymptomatic (i.e.,

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individuals with biallelic *ATP7B* pathogenic variants who have no clinical manifestations or tissue damage related to Wilson disease), clinically asymptomatic (i.e., individuals with biallelic *ATP7B* pathogenic variants who have no clinical manifestations of Wilson disease, but have Wilson disease-related tissue damage), or symptomatic (i.e., individuals with clinical manifestations of Wilson disease and Wilson disease-related tissue damage), regardless of age and including pregnant women. As Wilson disease treatment decisions might be complex, the consultation of disease experts (primarily hepatologists and neurologists) or Wilson disease centers of excellence is advised. The first-line therapy is copper chelating agents (D-penicillamine and trientine). Zinc salts (which interfere with absorption of copper from the gastrointestinal tract) cannot be used with a copper chelating agent and are most effective after initial decoppering with a chelating agent; however, in some individuals zinc salts can be used as an initial treatment. Orthotopic liver transplantation is used for individuals who fail to respond to medical therapy or present with fulminant acute liver failure.

The goals of supportive treatment for extrahepatic manifestations of individuals with symptomatic Wilson disease are individualized to maximize function and reduce complications. Depending on their clinical manifestations, symptomatic individuals may require specialists in neurology, occupational therapy, physical therapy, physiatry, orthopedics, nutrition, speech-language pathology, social work, and psychology/psychiatry.

Surveillance: To assess treatment effectiveness and adherence to medical interventions that prevent/treat copper accumulation, the following are recommended:

- At least twice annually: assessment of serum copper and ceruloplasmin levels, liver biochemistries, international normalized ratio, complete blood count, urinalysis, and physical examination including neurologic assessment
- At least once annually: measurement of 24-hour urinary excretion of copper

Monitoring the individual's response to supportive treatment for extrahepatic manifestations and the emergence of new manifestations is per the recommendations of the treating clinical specialists.

Agents/circumstances to avoid: Foods very high in copper (liver, brain, chocolate, mushrooms, shellfish, and nuts) should be avoided, especially at the beginning of treatment.

In case of biochemical abnormalities in liver function tests or transaminases, alcohol consumption is strongly discouraged.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of medical interventions to prevent/treat copper accumulation.

Pregnancy management: Treatment must be continued during pregnancy because of the risk for fulminant hepatic failure or irreversible neurologic deterioration. Because of possible adverse effects on the fetus from chelating agents, the dose should be kept as low as possible.

Genetic counseling

Wilson disease is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ATP7B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Once both *ATP7B* pathogenic variants have been identified in an affected family member, carrier and predictive genetic testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing for Wilson disease are possible.

Diagnosis

The diagnostic algorithm for Wilson disease in the European Association for Study of Liver (EASL) Clinical Practice Guidelines [European Association for Study of Liver 2012] is based on a diagnostic index ("Leipzig" score) proposed by an expert panel [Ferenci et al 2003]. This score includes clinical, biochemical, and molecular findings, but has not been validated in large patient series. The most recent diagnostic pathway of the American Association for Study of the Liver Diseases (AASLD) highlights diagnostic approaches when clinical and biochemical evaluations are ambiguous [Schilsky et al 2022b].

Suggestive Findings

Wilson disease **should be suspected** in individuals ages three to 45 years, but age alone should not exclude consideration of the diagnosis, as affected individuals have been diagnosed in their early 70s. At diagnosis, individuals with Wilson disease may have varying combinations of the following clinical findings, brain MRI findings (in those with neurologic manifestations), biochemical findings, and family history [Schilsky et al 2022b].

Clinical Findings

Children under age 18 years often present with hepatic disease exclusively.

Adults often present with hepatic disease with or without concurrent neuropsychiatric disease.

- **Liver disease** can range from recurrent jaundice, persistently elevated serum aminotransferase activity (AST, ALT), fatty liver, acute hepatitis (varying in severity, including acute liver injury), autoimmune-type hepatitis, and cirrhosis (compensated or decompensated) to acute liver failure (ALF).

Note: Specific instances when Wilson disease should be considered is ALF with nonimmune hemolytic anemia or autoimmune hepatitis.

- **Neurologic manifestations**, resulting from central nervous system damage as a result of copper storage, can include the following:
 - Dysarthria
 - Movement disorders (tremors, involuntary movements, chorea, choreoathetosis)
 - Dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement)
 - Dysautonomia
 - Seizures
 - Sleep disorders / insomnia
- **Psychiatric disturbances** can include depression, bipolar disorder / bipolar spectrum disorder, neurotic behaviors, personality changes, and psychosis.
- **Other extrahepatic involvement** can include the following:
 - Eye: Kayser-Fleisher rings, copper deposits in the periphery of the cornea, are observed by slit lamp examination and anterior segment optical coherence tomography (see Członkowska et al [2018], [Figure 8](#)). Sunflower cataracts and corneal nerve alterations can also occur.
 - Self-limited hemolytic anemia, with or without acute liver failure
 - Kidney abnormalities: aminoaciduria and nephrolithiasis
 - Hypoparathyroidism, pancreatitis
 - Cardiomyopathy, arrhythmias
 - Premature osteoporosis and arthritis
 - Infertility, recurrent miscarriages

Brain Imaging

Modalities such as magnetic resonance imaging (MRI) are of limited value in determining the extent of clinical neurologic disease but may help initially in supporting a diagnosis of Wilson disease and excluding other neurologic disorders.

Brain MRI findings consistent with Wilson disease include signal changes in the basal ganglia, thalami, pons, and white matter, as well as atrophy. Although the "face of the giant panda" sign (see Schilsky et al [2022b], Figure 1; [full text](#)), which consists of increased T₂ signal in the midbrain, has been considered pathognomonic for Wilson disease, several other findings are more commonly seen.

Biochemical Findings

Suggestive biochemical findings in a symptomatic individual relies on a combination of the following findings:

- 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 peak by age two to three years 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 (<0.2 g/L) and typically very low (<0.1 g/L).
Note: A normal serum ceruloplasmin concentration is found in at least 5% of individuals with Wilson disease with neurologic manifestations and up to 40% of individuals with hepatic findings [Steindl et al 1997]. Serum ceruloplasmin concentration is, therefore, not a reliable screening test for Wilson disease.
- **Low serum concentration of total copper.** Most individuals with Wilson disease have a subnormal serum copper concentration that is proportional to the serum ceruloplasmin concentration (as ceruloplasmin is the main copper transporter in blood). The copper bound to ceruloplasmin (i.e., ceruloplasmin-bound copper) is considered nontoxic.
Note: Serum copper is low in healthy newborns. The concentrations increase during the first six months of life and peak by age two to three years at a concentration that may exceed the healthy adult reference range.
- **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 agents) is almost invariably elevated above 40 µg or ~0.6 µmol/24 hours in most individuals with Wilson disease, and above 100 µg or ~1.6 µmol/24 hours in symptomatic individuals.
 - **A provocative test of urinary copper excretion** following oral administration of D-penicillamine has been validated only in pediatric cohorts, but has proven useful in some adults [Martins da Costa et al 1992]; however, levels in affected individuals can overlap with those of heterozygotes. Note: The use of a lower value for basal urinary copper excretion of 40 µg or ~0.6 µmol/24 hours increases diagnostic sensitivity and may obviate the need for the D-penicillamine provocation test.
- **Hepatic copper quantification.** Although liver biopsy is an invasive procedure, it can be helpful when clinical findings, biochemical findings, and/or molecular genetic test results are ambiguous. 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 as cholestatic conditions [Schilsky et al 2022b].

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 (100-250 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.

Family History

Family history is consistent with autosomal recessive inheritance. The family history may include affected sibs (e.g., sibs with liver disease, neurologic manifestations, and/or psychiatric disturbance) and/or parental consanguinity. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Wilson disease, using clinical, biochemical, and molecular genetic findings, is based on the diagnostic scoring system developed at the 8th International Meeting on Wilson Disease, Leipzig 2001 [Ferenci et al 2003, Członkowska et al 2018] (see Table 1).

Table 1. Diagnostic Scoring System for Wilson disease

Test	Parameter	Score
Typical clinical symptoms & signs		
Kayser-Fleischer rings	Present	2
	Absent	0
Neurologic manifestations ¹	Severe	2
	Mild	1
	Absent	0
Serum ceruloplasmin	Normal (>0.2 g/L)	0
	0.1-0.2 g/L	1
	<0.1 g/L	2
Coombs-negative hemolytic anemia	Present	1
	Absent	0
Other tests		
Liver copper (in the absence of cholestasis)	>250 µg (>4 µmol)/g dry weight	2
	50-249 µg (0.8–4 µmol)/g dry weight	1
	Normal: <50 µg (<0.8 µmol)/g dry weight	-1
	Rhodanine-positive granules ²	1
Urinary copper (in the absence of acute hepatitis)	Normal	0
	1-2x ULN	1
	>2x ULN	2
	Normal but >5x ULN after D-penicillamine	2

Table 1. continued from previous page.

Test	Parameter	Score
<i>ATP7B</i> molecular genetic testing	Biallelic pathogenic variants detected	4
	One pathogenic variant detected	1
	No pathogenic variants detected	0
Evaluation	Total score	
	Diagnosis established	≥4
	Diagnosis possible, more tests needed	3
	Diagnosis very unlikely	≤2

Adapted with permission from Ferenci et al [2003]

ULN = upper limit of normal

1. Or typical abnormalities on brain MRI

2. If no quantitative liver copper available

Per the diagnostic scoring system (see Table 1), the diagnosis of Wilson disease **can be established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *ATP7B* identified by molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ATP7B* variants of uncertain significance (or of one known *ATP7B* pathogenic variant and one *ATP7B* variant of uncertain significance) does not establish or rule out a diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) (see Option 1) and **comprehensive genomic testing** (exome sequencing, genome sequencing) (see Option 2). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Option 1

Single-gene testing. When clinical and biochemical findings strongly suggest the diagnosis of Wilson disease, sequence analysis of *ATP7B* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Targeted analysis can be performed first in individuals from populations with known founder variants (e.g., Ashkenazi Jewish, Canary Islands, Druze, Sardinia; see Table 7).

A multigene panel that includes *ATP7B* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 2. Molecular Genetic Testing Used in Wilson Disease

Gene ¹	Method	Proportion of Probands with Pathogenic Variants ² Detectable by Method
ATP7B	Sequence analysis ³	98% ⁴
	Gene-targeted deletion/duplication analysis ⁵	Rare ⁶

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Large deletions and duplications, encompassing one or more exons, are rare. Exon and multiexon deletions have been reported (see, e.g., Møller et al [2005], Incollu et al [2011], Møller et al [2011], Tatsumi et al [2011]).

Clinical Characteristics

Clinical Description

Untreated symptomatic Wilson disease can manifest in individuals ages three years to older than 70 years as hepatic, neurologic, psychiatric, or hematologic disturbances, or a combination of these. Phenotypic expression varies even within families. The understanding of the phenotypic spectrum has further expanded through the widespread use of molecular genetic testing, which has confirmed the diagnosis in individuals with atypical clinical and biochemical findings.

Table 3 outlines the typical presenting clinical findings of untreated Wilson disease. Of note, the "classic triad" of liver disease, movement disorder, and Kayser-Fleischer ring is uncommon.

Table 3. Clinical Findings in Individuals with Untreated Symptomatic Wilson Disease by Presenting Finding

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

Bruha et al [2011], Weiss et al [2011], Hofer et al [2012], Weiss et al [2013b]

Untreated Symptomatic Wilson Disease

Liver disease. Untreated Wilson disease manifests as liver disease more commonly in children and younger adults, typically between ages six and 45 years; however, severe liver disease can be the initial finding in preschool-aged children [Wilson et al 2000] and in older adults. The clinical manifestations vary and can include the following findings:

- **Recurrent jaundice**, possibly caused by hemolysis
- **Simple, acute, self-limited hepatitis-like illness** with fatigue, anorexia, and/or abdominal pain
- **Autoimmune hepatitis**, often manifesting 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

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 (abnormally small, cramped handwriting), chorea, and/or choreoathetosis.
- Spastic dystonia disorders manifest as 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 neurologic findings in individuals with a frank neurologic presentation, the neurologic findings in individuals with a hepatic presentation may be subtle. 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 may be observed.

In individuals with a neurologic presentation, extensive changes on brain imaging (such as evidence of tissue cavitation) suggest structural, irreversible brain damage. These individuals are less likely to improve with treatment [Sinha et al 2007].

Psychiatric manifestations are variable. Depression is common. Neurotic behavior includes phobias, compulsive behaviors, aggression, or antisocial behavior. Older individuals may have subtle psychopathology (e.g., progressive disorganization of personality with anxiety) and affective changes (e.g., labile mood and disinhibition). Pure psychotic disorders are uncommon.

Intellectual deterioration may also occur with poor memory, difficulty in abstract thinking, and shortened attention span.

Hemolytic anemia, with either acute or chronic hemolysis, indicates a high serum concentration of non-ceruloplasmin-bound copper, which leads to destruction of erythrocytes. Liver disease is likely to be present in such individuals, as are Kayser-Fleischer rings. Recurrent hemolysis predisposes to cholelithiasis, even in children.

Other extrahepatic involvement

- 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. They do not affect vision and are reduced or disappear with effective decoppering treatment (see Management).
- Kidney involvement: low molecular weight proteinuria, microscopic hematuria, Fanconi syndrome, aminoaciduria, and nephrolithiasis
- Arthritis: involvement of large joints from synovial copper accumulation
- Reduced bone mineral density with an increased prevalence of osteoporosis (in approximately 10% of affected individuals)
- 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; the estimated incidence is below 1% [Devarbhavi et al 2012].

Fertility and pregnancy. Most individuals with Wilson disease are fertile.

Successful pregnancies of women with Wilson disease who received treatment have been reported [Brewer et al 2000, Tarnacka et al 2000, Furman et al 2001]. Prior to diagnosis and treatment of Wilson disease, affected women may experience amenorrhea, infertility, or recurrent miscarriage [Członkowska et al 2018].

Treated Wilson Disease

The mainstay of treatment for Wilson disease remains lifelong oral pharmacotherapy and dietary copper restriction [Schilsky et al 2022b] (see Management, Medical Interventions to Prevent/Treat Copper Accumulation). Liver transplantation, which corrects the underlying hepatic defect in Wilson disease, is reserved for individuals with chronic or acute liver failure and those resistant to pharmacotherapy.

- **"Asymptomatic individuals with Wilson disease"** are those who have biallelic *ATP7B* pathogenic variants who are clinically asymptomatic and **do not have any Wilson disease-related tissue damage**. Typically these individuals are young infants, born to parents known to be carriers, identified by genetic testing during family screening. These children should remain asymptomatic on treatment, even if they have biochemical abnormalities but not Wilson disease-related tissue damage. (See Management, Evaluation of Relatives at Risk and Medical Interventions to Prevent/Treat Copper Accumulation.)
- **"Clinically asymptomatic individuals with Wilson disease"** are those who have biallelic *ATP7B* pathogenic variants who are clinically asymptomatic but **have Wilson disease-related tissue damage**. Treatment at this stage of disease is highly successful and is focused on stabilizing and reversing tissue injury and preventing the progression of symptoms.
- **Individuals with Wilson disease with symptomatic liver disease.** Improvement in synthetic function and clinical signs such as jaundice and ascites begins during the first two to six months of treatment, with further recovery possible over time.
- **Individuals with Wilson disease with neurologic or psychiatric manifestations.** Most stabilize within six to 18 months after initiation of consistent therapy. However, neurologic findings may not respond to medical treatment, and in a few instances individuals with preexisting neurologic findings might show a paradoxical worsening, with acceleration of neurologic involvement or development of new manifestations.

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *ATP7B* have been identified [Członkowska et al 2018, Ferenci et al 2019].

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 [Sandahl et al 2020].

In some population-based studies, the genetic prevalence was three to four times higher than clinically based estimates [Olivarez et al 2001, Coffey et al 2013], pointing to the complexity when classifying variants regarding its disease-causing potential and raising the question of whether penetrance is really 100%, as generally assumed.

Recent studies suggest a prevalence as high as one in 10,000, especially in isolated populations such as Sardinia [Gialluisi et al 2013].

Founder variants have been identified in persons of Ashkenazi Jewish and Druze heritage, as well as individuals from the Canary Islands and Sardinia (see Table 7).

Genetically Related Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ATP7B*.

Differential Diagnosis

The complete differential diagnosis of Wilson disease is extensive and includes:

- Copper metabolism disorders;
- Hereditary disorders involving the liver;
- Hereditary disorders involving the nervous system; and
- Acquired conditions such as viral hepatitis, severe drug toxicity, and nonalcoholic steatohepatitis (NASH).

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

Table 4 lists selected genetic disorders of interest in the differential diagnosis of Wilson disease (see also Schilsky et al [2022b], Table 5).

Table 4. Hereditary Disorders of Known Genetic Cause in the Differential Diagnosis of Wilson Disease

Gene(s)	Disorder	MOI	Copper Metabolism
Copper metabolism disorders			
<i>AP1S1</i>	MEDNIK syndrome (OMIM 609313)	AR	Low ceruloplasmin
<i>ATP7A</i>	Menkes disease (See ATP7A-Related Copper Transport Disorders .) ¹	XL	Low serum copper & low ceruloplasmin
	Occipital horn syndrome (See ATP7A-Related Copper Transport Disorders .)	XL	
	<i>ATP7A</i> -related distal motor neuropathy (See ATP7A-Related Copper Transport Disorders .)	XL	Normal
<i>CP</i>	Aceruloplasminemia ²	AR	Low ceruloplasmin
<i>SLC33A1</i>	Huppke-Brendel syndrome ³	AR	Low serum copper & low ceruloplasmin

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Copper Metabolism
Liver diseases ⁴			
<i>ABCB4</i>	MDR3 deficiency (PFIC3) (See Pediatric Genetic Cholestatic Liver Disease Overview .)	AR	Hepatic copper retention due to cholestasis
<i>HFE</i>	<i>HFE</i> hemochromatosis ⁵	AR	Hepatic copper retention due to cholestasis is possible.
<i>SERPINA1</i>	Alpha-1 antitrypsin deficiency ⁵	AD ⁶	
Neurologic disorders			
<i>ATN1</i>	DRPLA	AD	Normal
<i>DNAJC6</i> <i>FBXO7</i> <i>PARK7</i> <i>PINK1</i> <i>PRKN</i> <i>SYNJ1</i> <i>VPS13C</i>	Early-onset Parkinson disease (See Parkinson Disease Overview .)	AR	
<i>GCH1</i> <i>TOR1A</i>	Inherited forms of dystonia incl <i>DYT1</i> early-onset isolated dystonia & <i>GTPCH1</i> -deficient dopa-responsive dystonia	AD	
<i>HTT</i>	Huntington disease	AD	
<i>NPC1</i> <i>NPC2</i>	Niemann-Pick disease type C	AR	
Many genes ⁷	Hereditary ataxia	AD AR XL Mat ⁸	

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MOI = mode of inheritance; PFIC = progressive familial intrahepatic cholestasis; XL = X-linked

1. Onset during infancy
2. Iron overload due to lack of oxidase activity of ceruloplasmin
3. Characterized by cataract, sensorineural deafness, and severe developmental delay
4. Primary sclerosing cholangitis (OMIM 613806) and primary biliary cirrhosis (OMIM 109720) also present with abnormal liver biochemistries with or without hepatomegaly. The genetic basis of these disorders is unknown.
5. Presents with abnormal liver biochemistries with or without hepatomegaly
6. Alpha-1 antitrypsin deficiency is inherited in an autosomal codominant manner.
7. See Hereditary Ataxia Overview, [Causes](#).
8. The mode of inheritance depends on the genetic etiology of ataxia.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual with symptomatic untreated Wilson disease, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Symptomatic Untreated Wilson Disease

System/Concern	Evaluation	Comment
Primary manifestations		

Table 5. continued from previous page.

System/Concern	Evaluation	Comment	
Liver disease	Liver biopsy or biochemical testing & imaging of liver	<ul style="list-style-type: none"> Establish baseline copper studies (serum ceruloplasmin & serum copper & 24-hr urinary copper excretion). Consider additional upper GI endoscopy to exclude or confirm esophageal varices. 	
Neurologic	Neurologist assess for: <ul style="list-style-type: none"> Movement disorders Gait & balance disturbance 	Using validated neurologic rating scale (neurologic subscale of Unified Wilson's Disease Rating Scale) ¹	
Speech	For those w/dysarthria: eval by speech-language pathologist		
Musculoskeletal/ADL	Eval by physiatrist/OT/PT	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices	
Cognitive	Assess for cognitive dysfunction.		
Psychiatric	Eval by psychiatrist, psychologist, neuropsychologist if needed	For personality & mood disorders	
Eyes	Complete eye exam	To incl assessment for Kayser-Fleischer rings, sunflower cataracts	
Possible secondary manifestations			
Endocrine disorders	Glucose intolerance	Basic biochemical profile	Underlying liver disease might affect hormone metabolism.
	Parathyroid insufficiency		
	Disordered growth		
	Males: gynecomastia		
	Females: menstrual irregularity / amenorrhea		
	Frequent miscarriage		
Cardiac involvement	Cardiac arrhythmia	By cardiologist	
	Cardiomyopathy		
Renal involvement	By nephrologist	Assess for: <ul style="list-style-type: none"> Tubular dysfunction (e.g., aminoaciduria, hypercalcuria, hyperphosphaturia) Nephrolithiasis, nephrocalcinosis 	
Genetic counseling	By genetics professionals ²	To inform affected persons & their families re nature, MOI, & implications of Wilson disease to facilitate medical & personal decision making	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By treating clinicians, social workers	Assess need for: <ul style="list-style-type: none"> • Community or online resources; • Social work involvement for parental/caregiver support; • Home nursing referral.

ADL = activities of daily living; GI = gastrointestinal; OT = occupational therapist; PT = physical therapist

Adapted from Schilsky et al [2022b]

1. Członkowska et al [2007], Leinweber et al [2008]

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Medical Interventions to Prevent/Treat Copper Accumulation in Individuals with Wilson Disease Who Are Asymptomatic, Clinically Asymptomatic, or Symptomatic

See extensive review by the American Association for the Study of Liver Diseases [Schilsky et al 2022b] ([full text](#)) and EASL Clinical Practice Guidelines: Wilson's disease [European Association for Study of Liver 2012] ([full text](#)).

Individuals with Wilson disease can be clinically categorized as:

- "Asymptomatic" (individuals who have no clinical manifestations or tissue damage related to Wilson disease);
- "Clinically asymptomatic" (individuals who have no clinical manifestations of Wilson disease but have Wilson disease-related tissue damage); or
- "Symptomatic" (individuals who have clinical manifestations of Wilson disease and Wilson disease-related tissue damage).

The goal of therapy is to institute treatment with chelating agents as soon as possible in individuals with Wilson disease who are asymptomatic, clinically asymptomatic, or symptomatic.

- Treatment is lifelong, including during pregnancy.
- If one treatment is discontinued, an alternative modality must be substituted to prevent disease progression.
- Discontinuation of all treatment leads to hepatic and neurologic decompensation that is usually refractory to further medical intervention.
- During lifelong treatment, failure of any medication used to treat Wilson disease may occur, either at initiation of treatment or during maintenance therapy. Once concurrent disease and nonadherence are excluded, pharmacologic therapy should be re-evaluated and likely altered. For individuals who have more advanced liver disease or develop liver failure, evaluation for liver transplantation should be considered. Currently, no surrogate markers are established for evaluating treatment failure.

Asymptomatic individuals should be treated either with lower dosages (10-15 mg/kg) of a copper chelating agent (D-penicillamine or trientine) or zinc salts.

Clinically asymptomatic individuals should be treated with 15-20 mg/kg of a copper chelating agent (D-penicillamine or trientine).

Symptomatic individuals should be treated with 15-20 mg/kg of a copper chelating agent (D-penicillamine or trientine). However, some individuals with advanced liver disease may require more intensive therapy, and temporally separated combination therapy may be utilized.

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

- **D-penicillamine (chelator)**. Used since the 1950s as first-line therapy for Wilson disease [Durand et al 2001, Walshe 2003], D-penicillamine is given as tablets by mouth two or three times daily. Pyridoxine must be given along with D-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, noncompliance may be an issue, or body copper stores may have been adequately depleted.
 - Complete blood count and urinalysis must be monitored regularly during D-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. Evidence of any such side effects may require discontinuation of D-penicillamine and substitution of an alternate treatment. If such alternate therapies are unavailable, D-penicillamine-induced adverse events may be manageable by coadministration of steroids.
 - D-penicillamine inhibits collagen cross-linking and has some immunosuppressant properties. After decades of treatment, individuals may have abnormal skin and connective tissue collagen, and possible chronic depletion of copper and (possibly) other trace metals.
 - D-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, has been the usual second-line treatment for individuals who cannot tolerate D-penicillamine. However, a clinical trial of an alternative formulation, triethylene tetramine tetrahydrochloride, revealed good efficacy and better tolerance than D-penicillamine, supporting the concept of its use as first-line therapy [Schilsky et al 2022a].
 - Complete blood count and urinalysis must be monitored regularly in all individuals on trientine.
 - Rare side effects include gastritis with nausea and, in cases of overtreatment, iron deficiency anemia.
 - 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 five to six hours apart from the other, may be effective in severely decompensated hepatic Wilson disease [Santos Silva et al 1996, Askari et al 2003].

Zinc (metallothionein inducer). High-dose oral zinc interferes with absorption of copper from the gastrointestinal tract, presumably 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 individuals, it can be used as an initial treatment [Milanino et al 1992, Linn et al 2009].

Zinc is taken as tablets by mouth at least twice (usually 3 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. Increase of urinary copper excretion under zinc therapy may indicate insufficient treatment efficacy [Weiss et al 2011]. 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.

Restriction of foods very high in copper (liver, brain, chocolate, mushrooms, shellfish, and nuts) is likely prudent, especially at the beginning of treatment. It is recommended that individuals with special dietary needs (e.g., vegetarians) consult with a trained dietitian [Schilsky et al 2022b].

Orthotopic Liver Transplantation

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 2022b].

It remains controversial whether orthotopic liver transplantation should be a primary treatment for individuals with Wilson disease who have severe neurologic disease [Medici et al 2005, Weiss et al 2013a, Litwin et al 2022].

Supportive Treatment for Extrahepatic Manifestations

The goals of supportive treatment for extrahepatic manifestations of individuals with symptomatic Wilson disease are individualized to maximize function and reduce complications. Ideally each individual consults with multidisciplinary specialists in fields such as neurology, occupational therapy, physical therapy, psychiatry, orthopedics, nutrition, speech-language pathology, social work, and psychology/psychiatry, depending on the clinical manifestations.

Surveillance

Assessment of Treatment Effectiveness and Adherence to Medical Interventions to Prevent/Treat Copper Accumulation

Monitoring of individuals under therapy should include routine assessments of treatment efficacy by biochemical testing and clinical evaluation.

- Insufficient therapy, underdosage, or poor compliance could lead to reaccumulation of copper and development of new symptoms.
- Adverse events related to medical treatment (especially under D-penicillamine treatment) should be evaluated.
- Excessive long-term treatment could result in copper deficiency, leading to immobilization of iron (as observed in [aceruloplasminemia](#)) and neurologic symptoms of copper deficiency [Horvath et al 2010, da Silva-Júnior et al 2011].

According to current guidelines (AASLD [Schilsky et al 2022b] and EASL Clinical Practice Guidelines [European Association for Study of Liver 2012]), routine monitoring should include the following examinations:

- At least twice annually: serum copper and ceruloplasmin, liver biochemistries, international normalized ratio, complete blood count, urinalysis, and physical examination including neurologic assessment
Note: Individuals receiving chelation therapy require a complete blood count and urinalysis regularly, no matter how long they have been on treatment.
- At least once annually: 24-hour urinary excretion of copper
Note: Measurements are recommended more frequently if there are questions on compliance or if dosage of medications is adjusted.

Supportive Care

To monitor the individual's response to supportive care and the emergence of new manifestations, the evaluations in Table 6 are recommended based on the supportive treatment required by the individual.

Table 6. Recommended Surveillance of Extrahepatic Manifestations for Individuals with Symptomatic Wilson Disease

System/Concern	Evaluation	Frequency
Neurologic	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	At each visit
	Consider neuroimaging if new manifestations occur.	Per treating neurologist
Cognitive	Monitor educational needs.	At each visit
Speech & language	By speech-language pathologist & consideration of alternative means of communication	When clinically evident
Feeding	Eval of nutritional status & safety of oral intake	At each visit
Psychiatric/Behavioral	Behavioral assessment for depression, bipolar disorder, personality changes, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Foods very high in copper (liver, brain, chocolate, mushrooms, shellfish, and nuts) should be avoided, especially at the beginning of treatment.

In case of biochemical abnormalities in liver function tests or transaminases, alcohol consumption is strongly discouraged.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of medical interventions to prevent/treat copper accumulation (see Medical Interventions to Prevent/Treat Copper Accumulation). Asymptomatic and clinically asymptomatic individuals with Wilson disease should remain asymptomatic on treatment, even if they have biochemical abnormalities, histologic findings, or imaging evidence of organ damage. Evaluations can include:

- Molecular genetic testing if the *ATP7B* pathogenic variants in the family are known;
- If the *ATP7B* pathogenic variants in an affected family member are not known, biochemical assessment of parameters of copper metabolism (serum copper, urinary copper, ceruloplasmin) and liver function tests as well as ultrasound imaging of the liver (the finding of a "fatty liver" is common, even in young or asymptomatic individuals) and slit lamp examination for the presence of Kayser-Fleischer rings.

Note: Asymptomatic individuals with Wilson disease generally have a low serum concentration of ceruloplasmin and mildly increased basal 24-hour urinary copper excretion; however, sometimes asymptomatic individuals with Wilson disease cannot be easily distinguished from heterozygotes.

Although Wilson disease is an autosomal recessive disorder and the risk to the parents and offspring of a proband is low, screening of all first-degree relatives is recommended in order to ascertain clinically asymptomatic family members in whom treatment may prevent liver disease and other manifestations of Wilson disease [Schilsky et al 2022b].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy and Lactation Concerns

Pregnancy. Treatment must be continued during pregnancy because of the risk of fulminant hepatic failure and/or neurologic decline in the affected pregnant woman. Baseline biochemical and clinical assessment as soon as a pregnancy is recognized is important. This includes evaluation for portal hypertension in those who have cirrhosis because of the risk of peripartum variceal hemorrhage [Członkowska et al 2018].

- D-penicillamine has been used in many pregnancies with no adverse outcomes; however, congenital connective tissue disorders encompassing inguinal hernias and skin laxity have been reported in some exposed infants. Such adverse outcomes may depend on dose, which should be kept as low as possible while still preventing copper deficiency in the pregnant woman and accounting for the need for fetal copper during development [Członkowska et al 2018]. The dose of D-penicillamine should be maintained at the lowest effective dose during the first and second trimesters of pregnancy. Further reduction in dose may be considered in the third trimester – based on acceptable results of maternal biochemical liver function tests – to account for the increasing copper utilization by the growing fetus.
- Trientine has been used successfully during pregnancy, but the total number of reported individuals is small. Reduction of the dose to the lowest effective dose is recommended using a comparable approach to that for D-penicillamine.
- Zinc has been used effectively in pregnant women and typically does not require a decreased dose during pregnancy. However, changing medical therapy to zinc during pregnancy does not appear to decrease the risk of either miscarriage or adverse fetal outcomes [Członkowska et al 2018].

Lactation. All anti-copper medications appear to pass into breast milk, which can lead to copper deficiency in infants. Therefore, breastfeeding or using expressed maternal breast milk from a mother taking an anti-copper medication is not generally recommended [Członkowska et al 2018].

See [MotherToBaby](#) for further information on medication use during pregnancy and lactation.

Therapies Under Investigation

Tetrathiomolybdate (TTM) is an orally administered chelating agent proposed to work by multiple mechanisms [Plitz & Boyling 2019] including:

- Detoxifying non-ceruloplasmin-bound copper by creating a nonreactive tripartite complex with albumin and copper;
- Extracting copper from the endogenous cellular chelator metallothionein (based on its high affinity for copper); and
- Interfering with the intestinal uptake of copper when administered with food.

In a Phase II study [Weiss et al 2017], TTM effectively reduced non-ceruloplasmin-bound copper (corrected for copper-TTM-albumin complex) and improved clinical neurologic findings, without paradoxical neurologic worsening, as demonstrated by an overall improvement in Unified Wilson's Disease Rating Scale scores [Leinweber et al 2008]. Early elevation of serum aminotransferases in approximately 30% of individuals resolved with dose discontinuation or reduction; none developed evidence of drug-induced liver injury. Suitability for treating advanced hepatic Wilson disease requires further investigation. A Phase III trial of bis-choline TTM for Wilson disease is under way.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://european-clinical-trials-register.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Wilson disease is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for an *ATP7B* pathogenic variant.
- If a molecular diagnosis has been established in the proband, genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ATP7B* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
 - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
 - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Clinical disease is not known to occur in heterozygotes (carriers), although the possibility has not been adequately excluded at older ages. Note: Heterozygotes may have subclinical biochemical findings including low serum ceruloplasmin concentrations, borderline normal urinary copper, elevated urinary copper on provocative testing with D-penicillamine, and/or moderate elevation of hepatic copper (100-250 mg/g dry weight).

Sibs of a proband

- If both parents are known to be heterozygous for an *ATP7B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Clinical symptoms may vary between sibs (including monozygotic twins) with untreated Wilson disease. The range of clinical variability observed between sibs with the same biallelic *ATP7B* pathogenic variants and treated Wilson disease depends primarily on the age of diagnosis and treatment initiation, reflecting the period of exposure to copper overload conditions.
- Clinical disease is not known to occur in heterozygotes (carriers), although the possibility has not been adequately excluded at older ages. Note: Heterozygotes may have subclinical biochemical findings including low serum ceruloplasmin concentrations, borderline normal urinary copper, elevated urinary

copper on provocative testing with D-penicillamine, and/or moderate elevation of hepatic copper (100-250 mg/g dry weight).

Offspring of a proband

- Unless an affected individual's reproductive partner also has Wilson disease or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ATP7B*.
- Given the carrier rate of one in 90 in the general population, the likelihood that an affected individual will have an affected child is one in 180. A higher carrier frequency is observed in some population groups due to founder variants (see Prevalence).
- Because the risk that an individual with Wilson disease will have an affected child is low, testing of serum ceruloplasmin concentration after age one year should be an adequate screening in offspring of a proband, except in populations with a high incidence of Wilson disease and/or a high incidence of consanguinity. In these populations, molecular testing may be useful. If molecular testing is not performed, repeat biochemical testing (including ceruloplasmin and urinary copper excretion) of offspring is strongly encouraged if initial biochemical testing was performed before age three years.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ATP7B* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *ATP7B* pathogenic variants in the family.

Heterozygotes may have low serum ceruloplasmin concentrations, borderline normal urinary copper, elevated urinary copper on provocative testing with D-penicillamine, and/or moderate elevation of hepatic copper (100-250 mg/g dry weight), which make these tests unreliable in clarifying carrier status.

Related Genetic Counseling Issues

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 (see Management, Evaluation of Relatives at Risk).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for the reproductive partners of affected individuals and known carriers should be considered, particularly if consanguinity is likely and/or if both partners are of the same ethnic background. Founder variants have been identified in some populations (see Table 7).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *ATP7B* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for Wilson disease are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Association Bernard Pépin pour la Maladie de Wilson (ABPWilson)**

France

www.abpmaladiewilson.fr

- **Associazione Nazionale Malattida di Wilson**

Italy

www.malattidiwilson.org

- **Deutsche Leberhilfe e.V.**

Germany

www.leberhilfe.org/lebererkrankungen/morbus-wilson

- **Morbus Wilson e.V.**

Germany

www.morbus-wilson.de/de

- **Wilson Disease Association**

Phone: 866-961-0533; 414-961-0533

Email: info@wilsonsdisease.org

www.wilsonsdisease.org

- **Wilson's Disease Support Group - UK**

United Kingdom

www.wilsonsdisease.org.uk

- **American Liver Foundation**

Phone: 800-465-4837 (HelpLine)

www.liverfoundation.org

- **Canadian Liver Foundation**

Canada

Phone: 800-563-5483

Email: clf@liver.ca

www.liver.ca

- **Eurodis**

Rare Disease Europe

www.eurordis.org

- **Medline Plus**

[Wilson disease](#)

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Wilson Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>ATP7B</i>	13q14.3	Copper-transporting ATPase 2	ATP7B @ LOVD WilsonGen	ATP7B	ATP7B

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Wilson Disease ([View All in OMIM](#))

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

Molecular Pathogenesis

The product of *ATP7B* is copper-transporting ATPase 2, an intracellular transmembrane copper transporter that is key 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 gene is expressed mainly in the liver and kidneys.

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.

Mechanism of disease causation. Various pathogenic variants lead to different impairments in *ATP7B* function.

***ATP7B*-specific laboratory technical considerations.** Comprehensive *ATP7B* testing should include promotor variants, as assessment of exonic sequences only does not rule out the diagnosis of Wilson disease when biochemical and/or clinical features are consistent with the diagnosis.

Table 7. Notable *ATP7B* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000053.4	c.-436_-422delTGGCCGAGACCGCGG	--	Founder variant common in Sardinia [Loudianos et al 1999]

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000053.4 NP_000044.2	c.1934T>G	p.Met645Arg	Founder variants comprising 85% of pathogenic variants in persons of Ashkenazi Jewish ancestry [Shi et al 2017]
	c.3191A>C	p.Glu1064Ala	
	c.3207C>A	p.His1069Gln	
	c.2123T>C	p.Leu708Pro	Founder variant common in Gran Canaria, Canary Islands, Spain [García-Villarreal et al 2000]
	c.3649_3654 delGTTCTG	p.Val1217_Leu1218del	Founder variant in persons of Druze ancestry [Kalinsky et al 1998]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Michael Schilsky's clinical and research interests include transplant hepatology, acute liver failure, and inherited metabolic disorders of the liver, in particular Wilson disease and hemochromatosis. Dr Schilsky co-wrote the AASLD and EASL practice guidelines for Wilson disease and chaired the writing group for the newly released 2022 AASLD practice guidance on Wilson disease. He is author of numerous original manuscripts and reviews on the subject. He is the Principal Investigator on clinical trials of pharmacotherapy and gene therapy for Wilson disease. Dr Schilsky is the organizer and Principal Investigator for the multicenter, multinational registry trial for Wilson disease sponsored by the Wilson Disease Association with data coordinating center at Yale University. He is a member of the NIH-sponsored Acute Liver Failure Study Group. He currently serves as Chair of the Medical Advisory Committee for the Wilson Disease Association.

Dr Karl Heinz Weiss's clinical and research interests include transplant hepatology, Wilson disease, and liver tumors. Dr Weiss co-wrote the 2022 AASLD practice guidance on Wilson disease. He is author of numerous original manuscripts and reviews on the subject.

Drs Weiss and Schilsky are actively involved in clinical research regarding individuals with Wilson disease. They would be happy to communicate with persons who have any questions regarding diagnosis of Wilson disease or other considerations.

Contact Drs Weiss and Schilsky to inquire about review of *ATP7B* variants of uncertain significance. Both authors are also interested in hearing from clinicians treating families affected by Wilson disease in whom no causative variant has been identified.

Acknowledgments

MLS receives research support from the Wilson Disease Association (USA), Alexion, Orphalan, and Vivet Therapeutics. KHW receives research support from Morbus Wilson e.V., Alexion, Orphalan, Univar, and Vivet Therapeutics.

We would like to acknowledge the Wilson Disease Association for their support of patient care, research, and educational activities.

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Revision History

- 12 January 2023 (bp) Comprehensive update posted live
- 29 July 2016 (bp) Comprehensive update posted live
- 16 May 2013 (me) Comprehensive update posted live
- 24 January 2006 (me) Comprehensive update posted live
- 24 April 2003 (me) Comprehensive update posted live
- 22 October 1999 (me) Review posted live
- 12 May 1999 (dc) Original submission

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