Wilson Disease (ATP7B) Sequencing

Wilson disease (WD) is a rare inherited genetic disorder caused by pathogenic variants in the *ATP7B* gene, resulting in excessive amounts of copper accumulating in the body, particularly in the liver, brain, and eyes. Signs and symptoms most often appear during the teens but may appear as early as age 6 or as late as the mid-40s. Liver disease is typically the initial feature of Wilson disease in affected children and young adults. Nervous system or psychiatric problems are often the initial features in individuals diagnosed in adulthood, and commonly occur in young adults. Neurologic symptoms include clumsiness, tremors, difficulty walking, and speech problems. Psychiatric symptoms include impaired thinking, depression, anxiety, and mood swings. Individuals with Wilson disease may have copper deposits in the cornea that form a green to brown ring around the iris (Kayser-Fleischer ring). These individuals may demonstrate abnormalities in eye movement, such as the inability to look upward.

Disease Overview

Diagnosis

- Slit-lamp examination of cornea to detect Kayser-Fleischer rings
- Combination of biochemical findings:
  - Serum ceruloplasmin: low
  - Serum copper: low
  - Free copper: high
  - 24-hour urine copper: elevated
- Hepatic copper concentration on liver biopsy: elevated
- Testing *ATP7B* gene for variants can confirm diagnosis
  - Most reliable method of diagnosis
  - Can help determine if individual is presymptomatic or an unaffected carrier

Diagnostic Issues

- Affected individuals occasionally have normal biochemical test results
- Up to 20% of WD carriers have equivocal biochemical findings

Treatment

- Disease is fatal if untreated
- Treatment includes use of chelating agents to prevent or reverse symptoms
- Only cure is liver transplant

Genetics

Gene

ATP7B

Inheritance

Autosomal recessive

Penetrance

Age dependent, may be reduced

Tests to Consider

Biochemical and/or genetic testing may be used in evaluating individual for WD.

- Biochemical testing is more cost effective.
- Genetic testing has higher sensitivity and specificity.
- Combination of both is useful for diagnosis

Wilson Disease (ATP7B) Sequencing 3004411

Method: Massively Parallel Sequencing

Preferred test for genetic confirmation of Wilson disease or determination of carrier status

Related Tests

Ceruloplasmin 0050160

Method: Quantitative Immunoturbidimetry

May be used as initial screening test in WD or copper transport disorders

Copper, Serum or Plasma 0020096

Method: Quantitative Inductively Coupled Plasma-Mass Spectrometry

Useful in the assessment of deficiency or overload

Copper, Free, Serum or Plasma 3001971

Method: Quantitative Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)

- May be useful in the assessment of overload or response to copper-reducing therapies
- Directly measures the free (nonceruloplasmin bound) fraction of copper

Copper, Urine 0020461

Method: Quantitative Inductively Coupled Plasma-Mass Spectrometry

Useful in the assessment of overload

Copper, Random Urine 2011480

Method: Quantitative Inductively Coupled Plasma-Mass Spectrometry

Useful in the assessment of overload

Copper, Liver 0020694

Method: Quantitative Inductively Coupled Plasma-Mass Spectrometry

May be useful when related serum or urine assessments are inconclusive

Test Interpretation

Clinical Sensitivity

98%[1]

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	>99	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	>99	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	>99	62.1-100

[a]Gene included on this test is a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Results

Results as Reported in Patient Chart	Variant(s) Detected	Clinical Significance
Positive	Two pathogenic ATP7B gene variants detected on opposite chromosomes	Consistent with a diagnosis of WD
Negative	No pathogenic ATP7B variants detected	Significantly reduces the likelihood of being affected with or a carrier of WD
See note	One pathogenic ATP7B gene variant detected	Individual is at least a carrier of WD and may be affected with WD if an undetected variant is present on the opposite chromosome
	Variants of uncertain clinical significance may be identified	Uncertain

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated:
  - Regulatory region variants, including the Sardinian founder variant, c.-436_-422del15
  - Deep intronic variants
  - Large deletions/duplications
  - Variants in genes other than *ATP7B*

References

1. Stättermayer A, Zoller HM, Weiss KH, et al. Patients with Wilson disease without detectable ATP7B mutations. Abstract 464. Boston, MA: 65th Annual Meeting of the American Association for the Study of Liver Diseases. 2014.

Additional Resources

Coffey AJ, Durkie M, Hague S, et al. A genetic study of Wilson's disease in the United Kingdom. *Brain*. 2013;136(Pt 5):1476-1487.

Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. *Hepatology*. 2008;47(6):2089-2111.

Socha P, Janczyk W, Dhawan A, et al. Wilson's disease in children: a position paper by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;66(2):334-344.

Weiss KH. Wilson disease. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last update: Jul 2016; Accessed: Aug 2021]

Related Information

Wilson Disease
Wilson Disease Testing Algorithm

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review August 2021 | Last Update February 2022