Wilson Disease (ATP7B) Sequencing

Wilson disease is a rare inherited genetic disorder caused by 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 and 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 problem. Psychiatric symptoms include impaired thinking, depression, anxiety, and mood swings. Individuals with Wilson disease may have copper deposits in the cornea that forms 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-Fleisher 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 unaffected carrier

Diagnostic Issues

- Affected individuals occasionally have normal biochemical test results
- Up to 20% of WD carriers have equivocal biochemical findings
- *ATP7B* gene testing

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

Tests to Consider

Biochemical 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 2010716

Method: Polymerase Chain Reaction/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/Investigation

- 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

Inheritance

Autosomal recessive

Penetrance

Age dependent, may be reduced

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

Sensitivity/Specificity

- Clinical sensitivity: 98%[1]
- Analytical sensitivity/specificity: 99%

Results

- Positive
  - Two pathogenic *ATP7B* gene variants detected on opposite chromosomes
    - Consistent with a diagnosis of WD
  - One pathogenic *ATP7B* gene variant detected
    - Individual is at least a carrier of WD
    - May be affected with WD if an undetected variant is present on the opposite chromosome
- Negative
  - No pathogenic *ATP7B* variants detected
    - Significantly reduces likelihood patient is affected with or a carrier of WD
- Inconclusive
  - Variants of uncertain clinical significance may be identified

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated:
  - Regulatory region variants
  - Deep intronic variants
  - Large deletions/duplications
  - Variants in genes other than *ATP7B*

References

1. 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. PubMed

Additional Resources

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: Jun 2020]

Related Information

Wilson Disease
Wilson Disease Testing Algorithm