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

Prevalence
1/30,000-50,000

Age of Onset
Early childhood through late adulthood

Symptoms
Caused by toxic accumulation of copper in tissue
- Ophthalmologic disease
  - Kayser-Fleischer rings caused by copper deposits in the cornea
  - Liver disease
  - Hepatomegaly
  - Jaundice
  - Hepatitis
  - Cirrhosis
  - Chronic liver disease
  - Acute or end-stage liver failure

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

Most reliable testing method for genetic confirmation of WD or determination of carrier status

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

Copper, Urine 0020461
Method: Quantitative Inductively Coupled Plasma-Mass Spectrometry

Useful in the assessment of overload
- Neurologic disease
  - Progressive rigidity or abnormal movements (tremors, dystonia, dysartrhia)
  - Difficulty with gross and fine motor tasks
- Psychiatric disease
  - Mood disturbance (anxiety, depression, personality or behavioral changes)
  - Cognitive decline or memory problems

**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

**Diagnostic Issues**

- Affected individuals occasionally have normal biochemical test results
- Up to 20% of WD carriers have equivocal biochemical findings
- ATP7B gene testing
  - Most reliable method of diagnosis
  - Can help determine if individual is presymptomatic or unaffected carrier

**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
Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: 98%\(^1\)
- Analytical sensitivity/specificity: 99%

Results

- Positive
  - Two pathogenic \textit{ATP7B} gene variants detected on opposite chromosomes
    - Consistent with a diagnosis of WD
  - One pathogenic \textit{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 \textit{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 \textit{ATP7B}

References


Related Information

Wilson Disease
Wilson Disease Testing Algorithm