Wilson Disease (*ATP7B*) Sequencing

Indications for Ordering

- Confirm a diagnosis of Wilson disease (WD)
- Carrier testing for individuals with a family history of WD or reproductive partners of WD carriers
- Distinguish between affected and carrier status in individuals with equivocal biochemical findings

Test Description

Bidirectional sequencing of the entire *ATP7B* coding region and intron/exon boundaries

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

Primary test

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

Related tests

Wilson Disease Screening Panel, Serum 0020598

- Preferred panel to diagnose conditions of copper overload in symptomatic patients or individuals with a family history of WD
- Panel includes serum ceruloplasmin, serum copper, and free (direct) copper

Ceruloplasmin 0050160

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

Copper, Serum or Plasma 0020096

- Useful in the assessment of deficiency or overload

Copper, Serum Free (Direct) 0020596

- May be useful in the assessment of overload or response to copper-reducing therapies

Copper, Urine 0020461

- Useful in the assessment of overload

Copper, Random Urine 2011480

- Useful in the assessment of overload

Copper, Liver 0020694

- May be useful when related serum or urine assessments are inconclusive

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

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-Fleisher rings – caused by copper deposits in the cornea
- Liver disease
  - Hepatomegaly
  - Jaundice
  - Hepatitis
  - Cirrhosis
  - Chronic liver disease
  - Acute or end-stage liver failure
- Neurologic disease
  - Progressive rigidity or abnormal movements (tremors, dystonia, dysarthria)
  - 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

Phenotypic variability – inter- and intrafamilial

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 98% (Coffey, 2013)
- 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

- Coffey A, et al. A genetic study of Wilson's disease in the United Kingdom. Brain. 2013;136:1476-1487.
- Weiss KH. Wilson Disease. 1999 Oct 22 [Updated 2016 Jul 29]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. (www.ncbi.nlm.nih.gov/books/NBK1512/)