ATP7A-Related Copper Transport Disorders

Indications for Ordering

- Confirm causative variants in individuals symptomatic for
  - Menkes disease
  - Occipital horn syndrome (aka X-linked cutis laxa)
  - *ATP7A*-related distal motor neuropathy
- Determine carrier status of at-risk family members when familial variant is unknown

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of entire coding region and intron/exon boundaries of *ATP7A* gene
- Multiplex ligation-dependent probe amplification to detect large *ATP7A* deletions/duplications

Tests to Consider

Primary tests

ATP7A-Related Copper Transport Disorders (*ATP7A*) Sequencing and Deletion/Duplication 2008471

- Preferred molecular test for *ATP7A*-related copper transport disorders

ATP7A-Related Copper Transport Disorders (*ATP7A*), Sequencing 2007872

- Acceptable molecular test for ATP7A-related copper transport disorders
- Detects most pathogenic *ATP7A* gene variants but does not detect deletions or duplications

Related tests

Initial screening tests for *ATP7A* gene-related copper transport disorders

- Ceruloplasmin 0050160
- Copper, Serum Free (Direct) 0020596
- Catecholamines Fractionated, Plasma 0080216

Familial Mutation, Targeted Sequencing 2001961

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

Disease Overview

See table

Genetics

Gene – ATP7A

Inheritance – X-linked

Frequency – 1/100,000

Penetrance

- Menkes disease – 100%
- Occipital horn syndrome – 100% by adulthood

Physiology

- *ATP7A* gene codes for ATP7A protein, an ATP-dependent copper transporter expressed in almost all tissues except liver
- Severity of symptoms tends to relate to amount of residual enzyme activity
  - Menkes disease and occipital horn syndrome
    - Loss of function of ATP7A protein results in copper accumulation in intestinal mucosa and severe copper deficiency in multiple organs
    - Clinical spectrum ranges from classic Menkes disease (severe end of spectrum) to occipital horn syndrome to distal motor neuropathy (milder end of spectrum)
- *ATP7A*-related distal motor neuropathy
  - May be related to abnormal trafficking of ATP7A copper transporter

Variants

- Menkes disease variants tend to be profound loss-of-function variants
- Occipital horn syndrome variants allow for some residual copper transport
- *ATP7A*-related distal motor neuropathy variants are missense variants within or near luminal surface of protein
- Heterozygous females may be mildly symptomatic due to X-inactivation patterns, but are generally normal

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity
  - Unknown for *ATP7A*-related distal motor neuropathy
  - For Menkes disease and occipital horn syndrome
    - Sequencing with deletion/duplication – ~95%
    - Sequencing – ~80%
    - Deletion/duplication – ~15%
- Analytical sensitivity/specificity
  - Sequencing – 99%
  - Deletion/duplication – 99%/95%

Results

- Positive
  - One pathogenic variant in a male predicts Menkes disease, occipital horn syndrome, or *ATP7A*-related distal motor neuropathy
  - One pathogenic variant in a female confirms carrier status
    - Female carriers have variable presentations
- Negative – no pathogenic variant detected
  - Reduces the risk but does not exclude a diagnosis of Menkes disease, occipital horn syndrome, or *ATP7A*-related distal motor neuropathy
- Inconclusive – variants of unknown clinical significance may be detected
- Large *ATP7A* gene deletions in hemizygous males can result in the failure of sequencing reactions
  - In such cases, deletion/duplication analysis is recommended

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Not determined or evaluated
  - Regulatory region or deep intronic variants
  - Breakpoints of large deletions/duplications
  - Variants in genes other than *ATP7A*

Reference

Kaler SG. ATP7A-Related Copper Transport Disorders. 2003 May 9 [Updated 2010 Oct 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/books/NBK1413/)

Disease Overview

	Menkes disease	**Occipital horn syndrome (X-linked cutis laxa)**	***ATP7A*-related distal motor neuropathy**
Age of onset	Infancy	Infancy to early adulthood	Usually second or third decade of life, but may present in childhood or as late as sixth decade
Symptoms	• Subtle or nonspecific symptoms in first few months • Loss of milestones • Intellectual disability • Lethargy • Hypotonia • Seizures • Hypothermia • Feeding difficulties • Sparse, coarse, twisted, and lightly pigmented hair with texture like that of steel wool o Analysis of hair with light microscope shows pili torti, trichoclasis, and trichoptilosis • Other clinical findings o Wormian bones o Bladder diverticula o Tortuous blood vessels o Pectus excavatum o Skin laxity o Jowly appearance o Osteoporosis • Developmental disability • Very early treatment with copper histidine or chloride may o Enhance survival o Reduce seizure activity o Improve neurodevelopmental outcomes	• Shares many features with Menkes disease • Less severe neurological phenotype • Lax skin and joints • Bladder diverticula • Inguinal hernias • Vascular tortuosity • Mild intellectual disability • Dysautonomia and orthostatic hypotension (decreased dopamine beta-hydroxylase activity) • Occipital horns o Distinct, wedge-shaped calcifications in tendons that attach trapezius and sternocleidomastoid muscles to occipital bone o May be palpable or observed radiographically o Pathognomonic for condition	• Unlike Menkes disease and occipital horn syndrome • Atrophy and weakness of distal muscles in hands and feet • Foot drop with steppage gait • Mild proximal leg weakness • Hand and foot deformities o Curled fingers o Pes cavus • Symptoms typically slowly progressive – may resemble those of Charcot-Marie-Tooth disease
Related laboratory test results	• Copper (serum) – low • Ceruloplasmin (serum) – low • Dopamine/norepinephrine (serum, CSF) – elevated • Homovanillic acid/vanillylmandelic acid (urine) – elevated	• Copper (serum) – normal to low • Ceruloplasmin (serum) – normal to low • Dopamine/norepinephrine (serum, CSF) – normal to elevated • Homovanillic acid/vanillylmandelic acid (urine) – normal to elevated	• No biochemical abnormalities present • Nerve conduction tests – reduced compound motor amplitudes with generally normal conduction velocities