THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

ATP7A sequencing for Menkes disease and occipital horn syndrome

Clinical Features:

ATP7A mutations confer phenotypic heterogeneity by displaying two distinct disorders:

- Menkes disease [OMIM #309400]
  - Clinical findings: mental retardation, hypotonia, seizures, failure to thrive, vascular tortuosity, wormian bones, metaphyseal spurring, bladder diverticulae, pectus excavatum, skin laxity
  - Pathognomonic feature: pili torti
  - The mean survival is 3 years; major cause of death is respiratory failure secondary to pneumonia.

- Occipital Horn syndrome (OHS) or X-linked Cutis Laxa (formerly known as Ehlers-Danlos syndrome type IX) [OMIM #304150]
  - Clinical findings: bilateral occipital exostoses of the skull (occipital horns), long neck, high arched palate, long face, high forehead, skin and joint laxity, dysautonomia, bladder diverticula, inguinal hernias, vascular tortuosity, normal or slightly delayed intelligence
  - Pathognomonic feature: Pili torti
  - With appropriate treatment, survival is extended into adulthood.

These disorders are thought to be within the same spectrum of copper metabolism impairment, OHS being the milder of the two. Some patients exhibit *mild* Menkes disease with severity in the middle of this spectrum. Pili torti is usually present in all patients within the spectrum. Carrier females do not typically have symptoms, but ~50% have been reported to have patches of pili torti.

Diagnosis:

Copper levels are decreased in individuals with this spectrum of copper metabolism impairment (<60µg/dL). Ceruloplasmin levels are also diminished (30-150mg/L). Unfortunately, *healthy* newborns have copper and ceruloplasmin levels ranging between 20-70µg/dL and 50-220mg/L, respectively. For this reason, other clinical features must be taken into account while attempting to diagnose a newborn. Biochemical testing is unreliable for carrier testing (1).

Treatment:

Care is palliative and symptoms are treated as they appear. Treatment involving daily subcutaneous copper injections has been shown to reduce seizure frequency and decrease irritability if started *early* and administered for two years. Although this treatment has been practiced for over 30 years, it is not offered in the clinical setting, as controlled studies have not confirmed its benefit. There are research studies underway to better define the benefits of daily subcutaneous copper injections as well as to discover other treatment options (2).

Molecular Genetics:

ATP7A is located at Xq12-13, has 23 exons, and encodes a copper-transporting P-type ATPase (3). This gene is widely expressed and localizes to the trans-Golgi network in cells. Mutations identified in patients with Menkes disease include small insertions/deletions, nonsense mutations, missense abnormalities, splicing abnormalities, and large deletions/rearrangements (1). Sequence analysis of the coding region reveals >95% of mutations in males. Approximately 15% of mutations are deletions that may not be identified in a female carrier by sequencing. Mutations in patients with OHS tend to be less severe and allow for low levels of normal ATP7A transcript, thus resulting in the milder phenotype (4). Recently, intragenic duplications of one or more exons of *ATP7A* have been reported in approximately 5% of patients with Menkes disease (5).

Inheritance:

ATP7A is X-linked resulting in clinical features in affected males. One third of cases are *de novo*, the rest are inherited from a carrier female. A woman who has more than one affected son is an obligate carrier.

Testing Methods:

We offer full gene sequencing for all coding exons and the intron/exon boundaries of *ATP7A*. We also offer deletion/duplication analysis of the *ATP7A* gene by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. Deletion/duplication analysis will identify deletions in female carriers as well as duplications in males or females. The sensitivity of our deletion/duplication assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing.

ATP7A sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

ATP7A deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Kaler S. ATP7A-Related Copper Transport Disorders. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2003.
2. Kaler SG. Diagnosis and therapy of Menkes syndrome, a genetic form of copper deficiency. Am J Clin Nutr 1998: 67: 1029S-1034S.
3. Vulpe C, Levinson B, Whitney S et al. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. Nat Genet 1993: 3: 7-13.
4. Kaler SG, Gallo LK, Proud VK et al. Occipital horn syndrome and a mild Menkes phenotype associated with splice site mutations at the MNK locus. Nat Genet 1994: 8: 195-202.
5. Horn N, Biahri N, Moller L. Partial gene duplications in ATP7A accounts for 5% of the disease causing mutations in Menkes Disease. 11th International Congress of Human Genetics.

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