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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 to identify deletions/duplications of one or more exons. 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 mutation analysis (sequencing and deletion/duplication analysis)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2350
CPT codes:	83891, 83898 x 3, 83904 x 9, 83900, 83901 x 2, 83912
Turn-around time:	4 – 6 weeks

ATP7A sequence analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2025
CPT codes:	83891, 83898 x 4, 83904 x 9, 83912
Turn-around time:	4 – 6 weeks

ATP7A deletion/duplication analysis

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$350
CPT codes:	83891, 83900, 83912
Turn-around time:	4 weeks

Targeted analysis for a known sequence change in additional family members

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3 – 4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$550-590
CPT codes:	Call us for specific CPT codes
Turn-around time:	1 – 2 weeks

Molecular Diagnostics Laboratory Faculty and Staff:

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References:

1. Kaler SG. ATP7A-related Copper Transport Disorder. (2005) GeneReviews. www.genetests.com
2. Kaler SG. Diagnosis and therapy of Menkes syndrome, a genetic form of copper deficiency. (1998) *Am J Clin Nutr* 67(suppl): 1029S-34S.
3. Vulpe C, et al. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. (1993) *Nat Genet* 3(1): 7-13.
4. Kaler SG, et al. Occipital horn syndrome and a mild Menkes phenotype associated with splice site mutations at the MNK locus. (1993) *Nat Genet* 8(2): 195-202.
5. Hom N, Biahri N, Moller L. Partial gene duplications in ATP7A accounts for 5% of the disease causing mutations in Menkes disease. Abstract for presentation at [11th International Congress of Human Genetics](#).

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