



## ATP7A-Related Copper Transport Disorders

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### Summary

#### Clinical description

Menkes disease, occipital horn syndrome (OHS), and *ATP7A*-related distal motor neuropathy (DMN) are disorders caused by pathogenic variants in the *ATP7A*, the X-linked gene that encodes a copper-transporting ATPase. Classic Menkes disease typically presents after a six- to 12-week period of good health following a normal pregnancy and birth. Feeding difficulties and/or a seizure event are the usual initial presenting features. In the absence of a known or suspected positive family history, these issues prompt a diagnostic evaluation that may consume months, by which time hypotonia and significant neurodevelopmental delays are evident. OHS is milder neurologically and is not recognized until late childhood or adolescence. Both phenotypes involve subnormal serum copper levels and other manifestations of perturbed copper metabolism, including connective tissue weakness. In contrast, *ATP7A*-related DMN typically presents in early adulthood with isolated muscle weakness and atrophy, in the absence of overt copper metabolism abnormalities.

- While nonspecific temperature instability and hypoglycemia in the neonatal period may be noted retrospectively, infants with **classic Menkes disease** appear healthy until age 1.5 to three months, when loss of developmental milestones, hypotonia, seizures, and failure to thrive occur. The diagnosis is usually suspected when infants exhibit neurologic findings and concomitant characteristic changes of the hair (short, sparse, coarse, twisted, and often lightly pigmented). Without treatment, premature death is typical, often by age three years.
- **OHS** is characterized by "occipital horns," distinctive wedge-shaped calcifications at the sites of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone. Occipital horns may be clinically palpable or observed on skull radiographs. Individuals with OHS also have lax skin and joints, bladder diverticula, inguinal hernias, and vascular tortuosity. Intellect is normal or slightly reduced.
- ***ATP7A*-related DMN**, an adult-onset disorder resembling Charcot-Marie-Tooth disease, shares none of the clinical or biochemical abnormalities characteristic of Menkes disease or OHS.

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## Diagnosis/testing

Menkes disease and OHS are characterized by low concentrations of copper in some tissues as a result of impaired intestinal copper absorption, accumulation of copper in other tissues, and reduced activity of copper-dependent enzymes such as dopamine-beta-hydroxylase (DBH) and lysyl oxidase. While serum copper concentration and serum ceruloplasmin concentration are low in Menkes disease and OHS, they are normal in *ATP7A*-related DMN. Notably, serum copper and ceruloplasmin levels are low in healthy newborns for the first several months of life; thus, these are not reliable diagnostic biomarkers in infants younger than age two months.

The diagnosis of *ATP7A*-related copper transport disorders is most often confirmed in a proband by detection of either a hemizygous *ATP7A* pathogenic variant in a male or a heterozygous *ATP7A* pathogenic variant in a female with skewed X inactivation, or with a X-autosome translocation; the latter scenarios are quite rare.

## Management

*Prevention of primary manifestations (and treatment):* Subcutaneous injections of copper histidinate beginning by age 28 days (corrected for prematurity/gestational age) enhances survival and improves neurodevelopmental outcomes.

*Treatment of manifestations:*

- Classic Menkes disease. Seizure management per neurologist; early intervention and individualized education plan per developmental pediatrician, feeding therapy and gastrostomy tube placement to enhance caloric intake; antibiotic prophylaxis to prevent bladder infection and surgery for bladder diverticula; RSV, influenza and COVID vaccinations due to risk of recurrent pneumonia; social work support.
- Occipital horn syndrome. Possible droxidopa treatment for dysautonomia; early academic support and individualized education plan as indicated per developmental pediatrician; surgical treatment of bladder diverticula and antibiotic prophylaxis as necessary; physical therapy; joint splints per orthopedist or rheumatologist for joint laxity.
- *ATP7A*-related distal motor neuropathy. Special shoes with good ankle support; ankle-foot orthoses; physical therapy; occupational therapy; orthopedic surgery for severe *pes cavus* deformity; mobility devices; and exercise as tolerated.

*Surveillance:*

- Menkes disease. At each visit assess seizures, developmental progress, educational needs, growth and nutrition, therapy needs, mobility, self-help skills, frequency of pulmonary infections, and family needs.
- Occipital horn syndrome. At each visit assess orthostatic blood pressures, development, and educational needs. Annual pelvic ultrasound for bladder diverticula.
- *ATP7A*-related distal motor neuropathy. Annual neurologic exam, electroneurography of peripheral nerves, electromyography/electroneurography, physical therapy assessment, occupational therapy assessment, foot examination for pressure sores or poorly fitting footwear.

## Genetic counseling

The *ATP7A*-related copper transport disorders are inherited in an X-linked manner. Approximately one third of affected males have no family history of Menkes disease/OHS/DMN. If the mother is a heterozygote, the risk of transmitting the *ATP7A* pathogenic variant is 50% in each pregnancy: a male who inherits the pathogenic variant will be affected with the disorder present in his brother; females who inherit the pathogenic variant will be heterozygotes and generally will not be affected. Male Menkes disease survivors and males with OHS or *ATP7A*-related DMN theoretically could pass the pathogenic variant to all of their daughters and none of their

sons. When a pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

## GeneReview Scope

ATP7A-Related Copper Transport Disorders: Included Phenotypes

- Classic Menkes disease
- Occipital horn syndrome
- ATP7A-related distal motor neuropathy

For synonyms and outdated names see Nomenclature.

## Diagnosis

### Suggestive Findings

An ATP7A-related copper transport disorder (Menkes disease, occipital horn syndrome, or ATP7A-related distal motor neuropathy) **should be suspected** in individuals with the following clinical and laboratory findings.

### Clinical Findings

**Classic Menkes disease** is suspected in males who develop hypotonia, failure to thrive, and seizures between age six and twelve weeks.

Shortly thereafter, hair changes become manifest: the scalp and (usually) eyebrow hair is short, sparse, coarse, twisted, and often lightly pigmented (white, silver, or gray). The hair is shorter and thinner on the sides and back of the head. The hair can be reminiscent of steel wool cleaning pads. Light microscopic hair analysis reveals *pili torti* (hair shafts twisting 180°), trichoclasia (transverse fracture of the hair shaft), and trichoptilosis (longitudinal splitting of the hair shaft). Because of the flattening of the normal cylindrical structure, the periodicity of the twisting in *pili torti* is different from that found in naturally curly hair.

Specific clinical features include:

- Hypotonia and neurodevelopmental delays typically manifest by age three to six months
- Distinctive facial features: jowly appearance with sagging cheeks
- Pectus excavatum
- Skin laxity, particularly on the nape of the neck, axillae, and trunk
- Bladder diverticula that can result in bladder outlet obstruction
- Umbilical or inguinal hernias
- Autonomic dysfunction: dizziness, syncope (if ambulatory), chronic diarrhea
- Neck masses, usually representing internal jugular vein phlebectasia [Stevens et al 2020].

**Occipital horn syndrome (OHS)** is suspected in males with the following:

- Occipital horns (distinctive wedge-shaped calcifications at the site of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone). These calcifications may be clinically palpable or observed on skull radiographs.
- Lax skin and joints
- Bladder diverticula
- Inguinal hernias
- Vascular tortuosity
- Dysautonomia (chronic diarrhea, orthostatic hypotension)

- Mild cognitive deficits

**ATP7A-related distal motor neuropathy (DMN)**, an adult-onset DMN resembling [Charcot-Marie-Tooth hereditary neuropathy](#), shares none of the clinical or biochemical abnormalities characteristic of classic Menkes disease or OHS, and is characterized by the following:

- Progressive DMN with minimal or no sensory symptoms
- Distal muscle weakness and atrophy in the feet and hands with *pes cavus* foot deformities
- Deep tendon reflexes varying from normal to diminished, with frequently absent ankle reflexes
- Reduced compound motor amplitudes on nerve conduction tests with generally normal conduction velocities with positive waves and fibrillations on EMG

## Laboratory Findings

**Serum concentration of copper and ceruloplasmin.** Males with classic Menkes disease or OHS have low serum copper concentration and low serum ceruloplasmin concentration (see Table 1).

**Table 1.** Approximate Serum Copper and Ceruloplasmin Concentrations in Males with Menkes Disease, Occipital Horn Syndrome, and ATP7A-Related Distal Motor Neuropathy

Serum Concentration	Classic Menkes Disease <sup>1</sup>	Mild Menkes/OHS	ATP7A-Related DMN	Normal Ranges
<b>Copper</b>	<40 µg/dL	40-75 µg/dL	80-100 µg/dL	75-150 µg/dL; (birth - 3 mos: 20-70 µg/dL)
<b>Ceruloplasmin</b>	10-100 mg/L	120-220 mg/L	230-300 mg/L	200-450 mg/L; (birth - 3 mos: 50-200 mg/L)

OHS = occipital horn syndrome; DMN = distal motor neuropathy

1. Diagnosis of Menkes disease using serum copper and ceruloplasmin in males under eight weeks of age is problematic given the normally low serum concentration in healthy infants at this age. These levels rise steadily in early infancy for the latter group, in contrast to Menkes disease where the levels remain low if copper replacement therapy is not initiated.

## Establishing the Diagnosis

The diagnosis of ATP7A-related copper transport disorders is **most commonly established** in a proband by detection of either a hemizygous ATP7A pathogenic (or likely pathogenic) variant in a male or a heterozygous ATP7A pathogenic (or likely pathogenic) variant in a female on molecular genetic testing (Table 2) or by additional biochemical studies (see Additional Biochemical Studies) if molecular genetic test results are ambiguous.

Note: (1) The clinical/laboratory findings necessary to establish this diagnosis in a female proband are the same as for males (see Table 1). In some instances, a symptomatic female has an X-autosome translocation involving Xq21.1. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (3) Identification of a hemizygous or heterozygous ATP7A variant of uncertain significance does not establish or rule out the diagnosis.

## Molecular Genetic Testing

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ATP7A* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *ATP7A* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Table 2.** Molecular Genetic Testing Used in *ATP7A*-Related Copper Transport Disorders

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>ATP7A</i>	Sequence analysis <sup>3</sup>	80% <sup>4, 5</sup>
	Gene-targeted deletion/duplication analysis <sup>6</sup>	20% <sup>4</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Targeted next-generation sequencing of *ATP7A* on dried blood spots demonstrated >95% sensitivity for *ATP7A* pathogenic variants including four large deletions and duplications [Parad et al 2020].

6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

## Additional Biochemical Studies

In individuals with a compelling presentation for whom molecular genetic testing fails to identify a pathogenic variant in *ATP7A*, the following biochemical studies may be considered:

- **Plasma and CSF catecholamine analysis.** Plasma catechol concentrations are distinctively abnormal at all ages in males with classic Menkes disease and OHS, and normal in *ATP7A*-related DMN. Abnormal levels reflect partial deficiency of dopamine-beta-hydroxylase (DBH), a copper-dependent enzyme crucial for catecholamine biosynthesis.
- **Copper transport studies in cultured fibroblasts.** Impaired cellular copper exodus in Menkes disease can be demonstrated by increased cellular copper retention in pulse-chase experiments using radiolabeled copper in cultured fibroblasts (or amniocytes).

Note: This method is reserved for research situations or urgent prenatal testing when a family's *ATP7A* pathogenic variant is unknown. The latter situation has become exceedingly rare with the increased availability, accuracy, and efficiency of molecular genetic testing.

## Clinical Characteristics

### Clinical Description

The clinical spectrum of *ATP7A*-related copper transport disorders ranges from classic Menkes disease at the severe end, to occipital horn syndrome (OHS), to isolated distal motor neuropathy (DMN) [Kaler 2011]. Classic Menkes disease is characterized by neurodegeneration and failure to thrive commencing at age two to three months. The age at diagnosis is usually between four to eight months. In contrast, OHS presents in early-to-middle childhood and is characterized predominantly by connective tissue abnormalities. *ATP7A*-related DMN is an adult-onset disorder resembling [Charcot-Marie-Tooth hereditary neuropathy](#); it shares none of the clinical abnormalities characteristic of classic Menkes disease or OHS.

### Classic Menkes Disease

Infants appear healthy until age two to three months, when loss of early developmental milestones, hypotonia, seizures, and failure to thrive occur. Classic Menkes disease is usually first suspected when infants exhibit typical neurologic changes and concomitant characteristic changes of the hair (short, sparse, coarse, twisted, often lightly pigmented) and jowly appearance of the face.

Transient hypoglycemia, prolonged physiologic jaundice, and persistent temperature instability are nonspecific signs that may be noted in the neonatal period.

Vascular tortuosity, neck masses (due to internal jugular vein dilatation), bladder diverticula that can result in bladder outlet obstruction, and gastric polyps are not uncommon. Subdural hematomas and cerebrovascular accidents are also not uncommon.

Without early treatment with daily subcutaneous copper injections (and sometimes despite treatment), classic Menkes disease progresses to severe neurodegeneration and death, typically between ages seven months and 3.5 years. Cardiorespiratory failure, often precipitated by pneumonia, is a common cause of death.

### Imaging

- Brain MRI shows cerebral and cerebellar atrophy with ventriculomegaly, delayed myelination, and vascular tortuosity.
- MR angiography reveals a "corkscrew" appearance of cerebral vessels.
- Plain radiographs of the skull often reveal wormian bones. Metaphyseal spurring of long bones and rib fractures are also typical and may trigger concern regarding non-accidental trauma. In these instances, it is crucial to convey to social workers and other child protective services staff that these skeletal findings are consistent with the difficult natural history of this illness [Hill et al 2012].

### Mild Menkes Disease

A few affected individuals in whom motor and cognitive development are better than in classic Menkes disease have been described. Individuals with mild Menkes disease may walk independently and acquire formal language. Weakness, ataxia, tremor, and head-bobbing are characteristic neurologic findings. Seizures, if present, commence in mid- to late childhood; intellectual disability is mild. Connective tissue problems may be more prominent than in classic Menkes disease. *Pili torti* are present.



## Occipital Horn Syndrome (OHS; X-Linked Cutis Laxa)

Cognitive ability is within the normal range or slightly reduced. The predominant neurologic abnormalities in individuals with OHS are dysautonomia (e.g., orthostatic hypotension, chronic diarrhea) and subtle neurocognitive deficits. Lax skin and joints and bladder diverticula are common manifestations of lysyl oxidase (copper-dependent enzyme) deficiency. Elbow dislocations are not uncommon [Author, personal observation]. Inguinal hernias do not appear to occur at increased frequency in individuals with OHS. Scoliosis may occur with advancing age.

Little information exists on the full natural history of OHS or the fertility of affected individuals. An essentially normal life span appears likely.

## ATP7A-Related Distal Motor Neuropathy (DMN)

The age of onset ranges from as young as five years up to 60 years; most typically, the presenting features occur in the second or third decade of life [Kennerson et al 2010]. Findings include gradual atrophy and weakness of distal muscles in hands and feet, development of a foot drop with steppage gait, proximal weakness in the legs, and normal deep tendon reflexes or absent ankle reflexes. Sensory examination may be normal or show mild loss in the fingers and toes. The index case of the largest family reported had slow progression over 25 years, requiring ankle-foot orthoses at age 38 years [Kennerson et al 2009].

## Heterozygous Females

Females who are heterozygous for an *ATP7A* pathogenic variant are typically asymptomatic, in some instances because of favorably skewed X-chromosome inactivation [Desai et al 2011]. In theory, unfavorably skewed X-chromosome inactivation in some heterozygous females could be associated with neurologic or other clinical findings related to the disorders.

About 50% of females who are obligate heterozygotes for an *ATP7A* pathogenic variant demonstrate regions of *pili torti* [Moore & Howell 1985].

Evaluation of females who are obligate heterozygotes for an *ATP7A* pathogenic variant causing *ATP7A*-related DMN has been limited to date; however, in one family the clinical neurologic examinations and motor nerve conduction studies of the females proven to be heterozygous were normal [Kennerson et al 2009].

## Genotype-Phenotype Correlations

The amount of residual ATPase enzyme activity correlates with the phenotype in Menkes disease, OHS, and *ATP7A*-related distal motor neuropathy (DMN) and, in part, with response to early copper treatment in Menkes disease [Kaler et al 2008].

Milder variants of Menkes disease and OHS are often associated with splice junction pathogenic variants that alter but do not eliminate proper RNA splicing (i.e., "leaky" splice junction defects).

The pathogenic variants associated with *ATP7A*-related DMN involve unique missense variants within or near the luminal surface of the protein, which may be relevant to the abnormal intracellular trafficking shown for these defects and to the mechanism of this form of motor neuron disease [Kennerson et al 2010, Yi et al 2012, Yi & Kaler 2018]. Variants p.Phe1386Ser and p.Thr994Ile result in altered distribution of the protein, with preferential localization to the plasma membrane [Yi et al 2012]. The p.Thr994Ile variant exposes a hidden UBX domain that interacts avidly with vasolin-containing protein (p97/VCP) that has been linked to various membrane protein trafficking processes, including cargo sorting through the endosomal pathway [Yi & Kaler 2018].

Intrafamilial phenotypic variability is occasionally observed in Menkes disease [Kaler et al 1994, Borm et al 2004, Donsante et al 2007]. Differences noted among affected individuals from two families with *ATP7A*-related DMN included degree of weakness, atrophy, and sensory loss [Kennerson et al 2010].

## Nomenclature

Menkes disease is also known as Menkes kinky hair syndrome, or trichopolydystrophy.

Occipital horn syndrome was formerly known as X-linked cutis laxa.

*ATP7A*-related distal motor neuropathy is also known as X-linked distal spinal muscular atrophy 3.

## Prevalence

Previous estimates of the prevalence of Menkes disease were based on confirmed clinical cases ascertained from specific populations and varied from 1:40,000 to 1:354,507.

However, recent analyses based on genomic ascertainment of pathogenic alleles and assuming Hardy-Weinberg equilibrium predict a birth prevalence of *ATP7A*-related disorders potentially as high as 1:8,664 live male births [Kaler et al 2020].

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ATP7A*.

## Differential Diagnosis

**Menkes disease.** While classic Menkes disease often presents with a highly distinctive clinical and biochemical phenotype, a differential diagnosis may include other infantile-onset neurodevelopmental syndromes, including:

- [Biotinidase deficiency](#)
- [Organic acidurias](#)
- [Aminoacidurias](#)
- [Mitochondrial myopathies](#) (See [Mitochondrial Disorders Overview](#).)

**Occipital horn syndrome.** The differential diagnosis includes any conditions that involve skin and/or joint laxity, including:

- [FBLN5-related cutis laxa](#), inherited in an autosomal recessive or (less commonly) autosomal dominant manner and caused by pathogenic variants in *FBLN5*;
- [ELN-related cutis laxa](#), inherited in an autosomal dominant manner and caused by pathogenic variants in *ELN*;
- [EFEMP2-related cutis laxa](#).

***ATP7A*-related distal motor neuropathy.** The differential diagnosis includes other forms of [Charcot-Marie-Tooth hereditary neuropathy](#).

## Management

No formal clinical practice guidelines for *ATP7A*-related copper transport disorders have been published.



## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a male diagnosed with an *ATP7A*-related copper transport disorder, the evaluations summarized in Table 3a, 3b, and 3c (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3a.** Recommended Evaluations Following Initial Diagnosis in Individuals with Classic Menkes Disease Phenotype

System/Concern	Evaluation	Comment
<b>Neurologic</b>	Neurologic eval	<ul style="list-style-type: none"> <li>Incl brain imaging (MRI/MRA) to assess degree of cerebral/cerebellar atrophy.</li> <li>Consider EEG if seizures present.</li> <li>Assess for signs/symptoms of autonomic dysfunction (dizziness, syncope, chronic diarrhea).</li> </ul>
<b>Development</b>	Developmental assessment	<ul style="list-style-type: none"> <li>To incl gross motor, fine motor, personal-social, &amp; language development</li> <li>Eval for early intervention / special education &amp;/or PT, OT, &amp; speech therapy</li> </ul>
<b>Gastrointestinal/ Feeding</b>	Gastroenterology / nutrition / feeding team eval	<ul style="list-style-type: none"> <li>To incl eval of aspiration risk &amp; nutritional status</li> <li>Consider eval for gastrostomy tube placement in those w/ dysphagia &amp;/or aspiration risk.</li> <li>Evaluate for umbilical &amp;/or inguinal hernias.</li> <li>Evaluate for gastric polyps.</li> </ul>
<b>Bladder function</b>	Pediatric nephrology/urology	Pelvic ultrasound
<b>Pulmonary/ Immunology</b>	Assess for recurrent pneumonias	Chest radiographs (PA & lateral) if symptoms occur
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of Menkes disease to facilitate medical & personal decision making
<b>Family support &amp; resources</b>	Assess need for: <ul style="list-style-type: none"> <li>Community or online resources such as <a href="#">Parent to Parent</a>;</li> <li>Social work involvement for parental support;</li> <li>Home nursing referral.</li> </ul>	<ul style="list-style-type: none"> <li><a href="#">Menkes Foundation (UK)</a></li> <li><a href="#">The Menkes Foundation (USA)</a></li> <li><a href="#">Nos Enfants Menkes (France)</a></li> <li><a href="#">Angeli per la Vita (Italy)</a></li> </ul>

MOI = mode of inheritance; OT = occupational therapy; PA = posteroanterior; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

**Table 3b.** Recommended Evaluations Following Initial Diagnosis in a Male with Occipital Horn Syndrome

System/Concern	Evaluation	Comment
<b>Neurologic</b>	Neurologic eval	<ul style="list-style-type: none"> <li>To incl brain MRI/MRA for vascular tortuosity</li> <li>Assess for signs/symptoms of autonomic dysfunction (orthostatic hypotension, chronic diarrhea). <sup>1</sup></li> </ul>
<b>Development</b>	Developmental assessment	<ul style="list-style-type: none"> <li>To incl adaptive, cognitive, &amp; speech-language eval</li> <li>Evaluate need for additional educational support.</li> </ul>
<b>Bladder diverticula</b>	Pelvic ultrasound	
<b>Joint laxity</b>	Referral to pediatric rheumatologist	

Table 3b. continued from previous page.

System/Concern	Evaluation	Comment
<b>Genetic counseling</b>	By genetics professionals <sup>2</sup>	To inform affected persons & their families re nature, MOI, & implications of OHS to facilitate medical & personal decision making

MOI = mode of inheritance; OHS = occipital horn syndrome

1. Some medical centers have clinical autonomic testing laboratories.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

**Table 3c.** Recommended Evaluations Following Initial Diagnosis in a Male with *ATP7A*-Related Distal Motor Neuropathy

System/Concern	Evaluation	Comment
<b>Peripheral neuropathy</b>	Neurologic exam	To determine extent of weakness & atrophy, <i>pes cavus</i> , gait stability, & sensory loss
	EMG w/nerve conduction studies	To determine axonal form of neuropathy, severity, & involvement of sensory system
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: <ul style="list-style-type: none"> <li>Gross motor &amp; fine motor skills &amp; need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> <li>Feet for evidence of <i>pes cavus</i>, need for AFOs, specialized shoes</li> <li>Mobility, activities of daily living, &amp; need for adaptive devices</li> <li>Need for handicapped parking</li> </ul>
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	<ul style="list-style-type: none"> <li>To inform affected persons &amp; their families re nature, MOI, &amp; implications of <i>ATP7A</i>-related DMN to facilitate medical &amp; personal decision making</li> <li>Clinical screening of at-risk relatives based on X-linked inheritance</li> </ul>

AFOs = ankle-foot orthoses; DMN = distal motor neuropathy; EMG = Electromyography; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

**Table 4a.** Treatment of Manifestations in Individuals with Classic Menkes Disease

Manifestation/Concern	Treatment	Considerations/Other
<b>Seizures</b>	Standardized treatment w/ASM by experienced pediatric neurologist	<ul style="list-style-type: none"> <li>Many ASMs may be effective; none has been demonstrated effective specifically for this disorder.</li> <li>Education of parents/caregivers <sup>1</sup></li> </ul>
<b>Developmental delay / Intellectual disability</b>	<ul style="list-style-type: none"> <li>Early intervention incl OT, PT, &amp; speech therapy as indicated</li> <li>IEP</li> <li>Management by developmental pediatrician</li> </ul>	
<b>Poor weight gain / Failure to thrive</b>	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
<b>Bladder diverticula</b>	<ul style="list-style-type: none"> <li>Antibiotic prophylaxis regimen advised to prevent bladder infection</li> <li>Surgical resection if severe</li> </ul>	
<b>Recurrent pneumonia</b>	<ul style="list-style-type: none"> <li>Gastrostomy tube feeds to ↓ risk of aspiration pneumonia</li> <li>Vaccination against RSV, influenza, &amp; COVID</li> </ul>	Home oxygen, BiPAP &/or tracheostomy, as indicated

Table 4a. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
<b>Family/Community</b>	<ul style="list-style-type: none"> <li>• Ensure appropriate social work involvement to connect families w/local resources, respite, &amp; support.</li> <li>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, &amp; supplies.</li> </ul>	Ongoing assessment of need for palliative care involvement &/or home nursing

ASM = anti-seizure medication; IEP = individualized education plan; OT = occupational therapy; PT = physical therapy

Table 4b. Treatment of Manifestations in a Male with Occipital Horn Syndrome

Manifestation/Concern	Treatment	Considerations/Other
<b>Dysautonomia</b>	Possible droxidopa (Northera®) therapy	See Therapies Under Investigation.
<b>Developmental delay / Intellectual disability</b>	<ul style="list-style-type: none"> <li>• Early academic support / IEP as indicated</li> <li>• Management by developmental pediatrician</li> </ul>	
<b>Bladder diverticula</b>	<ul style="list-style-type: none"> <li>• Surgical treatment</li> <li>• Antibiotic prophylaxis may be necessary to prevent bladder infection.</li> </ul>	
<b>Joint laxity</b>	<ul style="list-style-type: none"> <li>• Physical therapy</li> <li>• Joint splints if recommended by orthopedic or rheumatology expert.</li> </ul>	

IEP = individualized education plan

Table 4c. Treatment of Manifestations in a Male with ATP7A-Related Distal Motor Neuropathy

Manifestation/Concern	Treatment
<b>Neuropathy</b>	<ul style="list-style-type: none"> <li>• Special shoes, incl those w/good ankle support</li> <li>• AFOs to correct foot drop &amp; aid walking</li> <li>• PT (strength &amp; stretching exercises)</li> <li>• OT</li> <li>• Orthopedic surgery to correct severe <i>pes cavus</i> deformity if recommended by expert orthopedist or rheumatologist</li> <li>• Forearm crutches, canes/walkers for gait stability, &amp; wheelchairs</li> <li>• Exercise w/in person's capability (Many remain physically active.)</li> </ul>

AFOs = ankle-foot orthoses; OT = occupational therapy; PT = physical therapy

## Prevention of Primary Manifestations

**Menkes disease.** In classic Menkes disease, early treatment with subcutaneous injections of copper histidinate (CuHis), ideally within four weeks of birth (corrected for prematurity/gestational age) often enhances survival and improves quality of neurodevelopmental outcome [Kaler et al 2008; Kaler et al 2010; Kaler et al, unpublished data]. However, some infants may not show significant improvement relative to the natural history of untreated Menkes disease [Kaler et al 1995; Kaler et al 2008; Kaler et al, unpublished data]. The type and severity of the *ATP7A* pathogenic variant may partly influence response to early copper treatment [Kaler et al 2008].

To maintain serum copper concentration in the normal range (75-150 µg/dL), the suggested dose of copper histidinate (CuHis) is:

- For infants age <1 year: 250 µg administered subcutaneously (0.5 mL) 2x/day
- For infants age ≥1 year: 250 µg administered subcutaneously (0.5 mL) 1x/day

Cupric chloride (CuCl<sub>2</sub>) is available commercially in a concentration of 200 µg/0.5 mL for intravenous administration as a total parenteral nutrition additive. CuCl<sub>2</sub> has been used for subcutaneous injections in

urgent situations to raise circulating copper levels in affected newborns with Menkes disease for whom CuHis was not immediately available. However, the highly acidic pH (2.1) renders this formulation unsuitable for long-term subcutaneous use due to local skin irritation and considerable scarring.

Any role for subcutaneous CuCl<sub>2</sub> in Menkes disease should be eliminated when CuHis is approved by regulatory authorities in the US and other countries.

**Occipital horn syndrome.** Although there is no evidence that copper replacement therapy for OHS is clinically beneficial; in the authors' opinion it is reasonable to expect even better neurodevelopmental and neurocognitive outcomes if individuals with OHS were identified early and treated with CuHis during their first three years of life.

## Surveillance

For infants being treated with CuHis (or temporarily with CuCl<sub>2</sub>), monitor serum copper and ceruloplasmin levels to avoid supranormal levels.

**Table 5a.** Recommended Surveillance for a Male with Menkes Disease

System/Concern	Evaluation	Frequency
<b>Neurologic</b>	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations such as seizures, changes in tone, movement disorders.	
<b>Development</b>	Monitor developmental progress & educational needs.	At each visit
<b>Growth/ Nutrition</b>	<ul style="list-style-type: none"> <li>• Measurement of growth parameters (weight, length, head circumference)</li> <li>• Eval of nutritional status &amp; safety of oral intake</li> </ul>	
<b>Musculoskeletal</b>	Physical medicine, OT/PT assessment of mobility, self-help skills	
<b>Respiratory</b>	Assess for recurrent pulmonary infections.	
<b>Family/ Community</b>	Assess family need for social work support (e.g., home nursing, other local resources; coordination of care; need for palliative/respite care).	At each visit

OT = occupational therapy; PT = physical therapy

**Table 5b.** Recommended Surveillance for a Male with Occipital Horn Syndrome

System/Concern	Evaluation	Frequency
<b>Autonomic dysfunction (dizziness, syncopal episodes)</b>	Consider orthostatic blood pressures (supine & standing).	At each visit
<b>Development</b>	Monitor developmental progress & educational needs.	
<b>Bladder diverticula</b>	Pelvic ultrasound	Annually

**Table 5c.** Recommended Surveillance for a Male with ATP7A-Related Distal Motor Neuropathy

System/Concern	Evaluation	Frequency
<b>Neurologic</b>	<ul style="list-style-type: none"> <li>• Neurologic exam</li> <li>• Electroneurography of peripheral nerves</li> <li>• EMG/ENG</li> </ul>	Annually
	<b>Musculoskeletal</b>	
<b>Foot exam</b>	For pressure sores or poorly fitting footwear	

EMG = electromyography; ENG = electroneurography; OT = occupational therapy; PT = physical therapy

## Evaluation of Relatives at Risk

It is appropriate to test male relatives at risk for Menkes disease for the *ATP7A* pathogenic variant identified in the family before age ten days in order to promptly begin copper replacement treatment (see Prevention of Primary Manifestations).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

CuHis received FDA FastTrack (2018) and Breakthrough (2020) designations from the US Food and Drug Administration and the European Medicines Agency Committee for Orphan Medicinal Products issued a positive opinion for Orphan Drug Designation in 2020. An expanded access clinical trial that provides CuHis for individuals with Menkes disease in the US (NCT04074512) is currently in progress.

For updated preliminary results on subcutaneous CuHis treatment for Menkes disease, click [here](#).

Adeno-associated viral (AAV) gene therapy in combination with copper has also been investigated in Menkes disease mouse models, with promising results [Donsante et al 2011, Haddad et al 2018].

Newborn screening is not currently available for Menkes disease because biochemical strategies may not be compatible with or practical for current newborn screening platforms. A pilot study to evaluate the potential of sequence analysis of *ATP7A* from dried blood spots demonstrated proof of principle for this approach [Parad et al 2020]. If successful, such testing would allow early diagnosis and treatment of Menkes disease and other *ATP7A*-related disorders.

A Phase I/II clinical trial of droxidopa (Northera<sup>®</sup>) for dysautonomia in adult survivors of Menkes disease and adults with occipital horn syndrome is scheduled to open in Spring, 2021, using a double-blind placebo-controlled randomized crossover design.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Other

Therapies proven to be ineffective include vitamin C.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*ATP7A*-related copper transport disorders (i.e., classic Menkes disease, occipital horn syndrome [OHS], and *ATP7A*-related distal motor neuropathy [DMN]) are inherited in an X-linked manner.

## Risk to Family Members

**Parents of a male proband**

- The father of an affected male will not have the disorder nor will he be hemizygous for the *ATP7A* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *ATP7A* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have a *de novo ATP7A* pathogenic variant (in which case the mother is not heterozygous), or the mother may have somatic/germline mosaicism.

About one third of affected males represent simplex cases.

- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *ATP7A* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected. Intrafamilial phenotypic variability is occasionally observed in Menkes disease and may also be observed in *ATP7A*-related DMN (see Genotype-Phenotype Correlations).
  - Females who inherit the pathogenic variant will be heterozygotes. About 50% of females who are obligate heterozygotes for an *ATP7A* pathogenic variant demonstrate regions of *pili torti* but are otherwise generally asymptomatic (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and if the *ATP7A* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism.

### Offspring of a male proband

- Male Menkes disease survivors, and males with OHS, or *ATP7A*-related DMN transmit the *ATP7A* pathogenic variant to all of their daughters and none of their sons.
- Males with classic Menkes disease are not known to reproduce.

**Other family members.** The maternal aunts and maternal cousins of a male proband may be at risk of being heterozygous for an *ATP7A* pathogenic variant.

## Heterozygote Detection

**Molecular genetic testing.** Identification of female heterozygotes requires either prior identification of the *ATP7A* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

About 50% of females who are obligate heterozygotes for an *ATP7A* pathogenic variant demonstrate regions of *pili torti* but are otherwise generally asymptomatic (see Clinical Description, Heterozygous Females).

Note: Biochemical testing is generally unreliable for carrier detection because of overlap with normal ranges.



## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being heterozygous or affected.

**DNA banking.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Once the *ATP7A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Association Nos Enfants Menkes**  
France  
**Email:** [nosenfantsmenkes@gmail.com](mailto:nosenfantsmenkes@gmail.com)  
[www.nosenfantsmenkes.com](http://www.nosenfantsmenkes.com)
- **Associazione Angeli**  
Italy  
**Email:** [info@angeliperlavita.info](mailto:info@angeliperlavita.info)  
[www.angeliperlavita.info](http://www.angeliperlavita.info)
- **Medline Plus**  
[Menkes syndrome](#)
- **National Institute of Neurological Disorders and Stroke (NINDS)**  
PO Box 5801  
Bethesda MD 20824  
**Phone:** 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)  
[Menkes Disease Information Page](#)
- **NCBI Genes and Disease**  
[Menkes syndrome](#)

## Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

**Table A.** ATP7A-Related Copper Transport Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">ATP7A</a>	<a href="#">Xq21.1</a>	<a href="#">Copper-transporting ATPase 1</a>	<a href="#">ATP7A @ LOVD</a>	<a href="#">ATP7A</a>	<a href="#">ATP7A</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for ATP7A-Related Copper Transport Disorders ([View All in OMIM](#))

<a href="#">300011</a>	<a href="#">ATPase, Cu(2+)-TRANSPORTING, ALPHA POLYPEPTIDE; ATP7A</a>
<a href="#">300489</a>	<a href="#">NEURONOPATHY, DISTAL HEREDITARY MOTOR, X-LINKED; HMNX</a>
<a href="#">304150</a>	<a href="#">OCCIPITAL HORN SYNDROME; OHS</a>
<a href="#">309400</a>	<a href="#">MENKES DISEASE; MNK</a>

## Molecular Pathogenesis

The protein encoded by *ATP7A*, a P-type ATPase, transports copper across cellular membranes and is critical for copper homeostasis.

*ATP7A* pathogenic variants may result in a gene product with no copper transport capability (usually associated with a severe phenotype) or reduced quantity of normally functioning gene product (can be associated with a milder phenotype).

Most *ATP7A* pathogenic variants are family specific (unique), although certain variants have occurred in more than one family (e.g., exon 1 deletion, Gly666Arg, Gly727Arg). *ATP7A* variant types include: deletions and duplications; insertions; and nonsense, splice junction, and missense variants.

*ATP7A*-related distal motor neuropathy involves several unique pathogenic missense variants within or near the luminal surface of the protein [Kennerson et al 2010], which may be relevant to the abnormal intracellular trafficking shown for these defects and the mechanism of this form of motor neuron disease.

### Mechanism of disease causation

- **Menkes disease, OHS.** Loss of copper transport function
- ***ATP7A*-related isolated DMN.** Uncertain

***ATP7A*-specific laboratory technical considerations.** Deep intronic variants may be difficult to detect by commercial molecular diagnostic laboratories [Parad et al 2020].

**Table 6.** Notable *ATP7A* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000052.7 NP_000043.4	c.2981C>T	p.Thr994Ile	See Genotype-Phenotype Correlations.
	c.4156C>T	p.Phe1386Ser	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

### Author Notes

[www.nationwidechildrens.org/specialties/menkes-disease-clinic](http://www.nationwidechildrens.org/specialties/menkes-disease-clinic)

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- 27 November 2002 (sk) Original submission

## References

### Literature Cited

- Borm B, Moller LB, Hausser I, Emeis M, Baerlocher K, Horn N, Rossi R. Variable clinical expression of an identical mutation in the *ATP7A* gene for Menkes disease/occipital horn syndrome in three affected males in a single family. *J Pediatr*. 2004;145:119–21. PubMed PMID: 15238919.
- Desai V, Donsante A, Swoboda KJ, Martensen M, Thompson J, Kaler SG. Favorably skewed X-inactivation accounts for neurological sparing in female carriers of Menkes disease. *Clin Genet*. 2011;79:176–82. PubMed PMID: 20497190.
- Donsante A, Tang JR, Godwin SC, Holmes CS, Goldstein DS, Bassuk A, Kaler SG. Differences in *ATP7A* gene expression underlie intra-familial variability in Menkes disease/occipital horn syndrome. *J Med Genet*. 2007;44:492–7. PubMed PMID: 17496194.
- Donsante A, Yi L, Zerfas P, Brinster L, Sullivan P, Goldstein DS, Prohaska J, Centeno JA, Kaler SG. *ATP7A* gene addition to the choroid plexus results in long-term rescue of the lethal copper transport defect in a Menkes disease mouse model. *Mol Ther*. 2011;19:2114–23. PubMed PMID: 21878905.

- Haddad MR, Choi EY, Zerfas PM, Yi L, Martinelli D, Sullivan P, Goldstein DS, Centeno J, Brinster L, Ralle M, Kaler SG. Cerebrospinal fluid-directed rAAV9-rsATP7A plus subcutaneous copper histidinate advance survival and outcomes in a Menkes disease mouse model. *Mol Ther Methods Clin Dev.* 2018;10:165–78. PubMed PMID: 30090842.
- Hill SC, Dwyer AJ, Kaler SG. Cervical spine anomalies in Menkes disease: a radiologic finding potentially confused with child abuse. *Pediatr Radiol.* 2012;42:1301–4. PubMed PMID: 22825777.
- Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. *J Community Genet.* 2022;13:389–97. PubMed PMID: 35834113.
- Kaler SG. The neurology of ATP7A copper transporter disease: emerging concepts and future trends. *Nat Rev Neurol.* 2011;7:15–29. PubMed PMID: 21221114.
- Kaler SG, Buist NR, Holmes CS, Goldstein DS, Miller RC, Gahl WA. Early copper therapy in classic Menkes disease patients with a novel splicing mutation. *Ann Neurol.* 1995;38:921–8. PubMed PMID: 8526465.
- Kaler SG, Ferreira CR, Yam LS. Estimated genetic prevalence of Menkes disease based on the Genome Aggregation Database (gnomAD). *Mol Genet Metab Rep.* 2020;24:100602. PubMed PMID: 32528851.
- Kaler SG, Gallo LK, Proud VK, Percy AK, Mark Y, Segal NA, Goldstein DS, Holmes CS, Gahl WA. Occipital horn syndrome and a mild Menkes phenotype associated with splice site mutations at the MNK locus. *Nat Genet.* 1994;8:195–202. PubMed PMID: 7842019.
- Kaler SG, Holmes CS, Goldstein DS, Tang JR, Godwin SC, Donsante A, Liew CJ, Sato S, Patronas N. Neonatal diagnosis and treatment of Menkes disease. *N Engl J Med.* 2008;358:605–14. PubMed PMID: 18256395.
- Kaler SG, Liew CJ, Donsante A, Hicks JD, Sato S, Greenfield JC. Molecular correlates of epilepsy in early diagnosed and treated Menkes disease. *J Inher Metab Dis.* 2010;33:583–9. PubMed PMID: 20652413.
- Kennerson M, Nicholson G, Kowalski B, Krajewski K, El-Khechen D, Feely S, Chu S, Shy M, Garbern J. X-linked distal hereditary motor neuropathy maps to the DSMAX locus on chromosome Xq13.1-q21. *Neurology.* 2009;72:246–52. PubMed PMID: 19153371.
- Kennerson ML, Nicholson GA, Kaler SG, Kowalski B, Mercer JF, Tang J, Llanos RM, Chu S, Takata RI, Speck-Martins CE, Baets J, Almeida-Souza L, Fischer D, Timmerman V, Taylor PE, Scherer SS, Ferguson TA, Bird TD, De Jonghe P, Feely SM, Shy ME, Garbern JY. Missense mutations in the copper transporter gene ATP7A cause X-linked distal hereditary motor neuropathy. *Am J Hum Genet.* 2010;86:343–52. PubMed PMID: 20170900.
- Moore CM, Howell RR. Ectodermal manifestations in Menkes disease. *Clin Genet.* 1985;28:532–40. PubMed PMID: 4075564.
- Parad RB, Kaler SG, Mauceli E, Sokolsky T, Yi L, Bhattacharjee A. Targeted next generation sequencing for newborn screening of Menkes disease. *Mol Genet Metab Rep.* 2020;24:100625. PubMed PMID: 32714836.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405–24. PubMed PMID: 25741868.
- Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. *Hum Genet.* 2020;139:1197–207. PubMed PMID: 32596782.
- Stevens KE, Price JE, Marko J, Kaler SG. Neck masses due to internal jugular vein phlebectasia: frequency in Menkes disease and literature review of 85 pediatric cases. *Am J Med Genet Part A.* 2020;182:1364–77. PubMed PMID: 32293788.

Yi L, Donsante A, Kennerson ML, Mercer JFB, Garbern JY, Kaler SG. Altered intracellular localization and valosin-containing protein (p97 VCP) interaction underlie ATP7A-related distal motor neuropathy. *Hum Mol Genet.* 2012;21:1794–807. PubMed PMID: 22210628.

Yi L, Kaler SG. Interaction between the AAA ATPase p97/VCP and a concealed UBX domain in the copper transporter ATP7A is associated with motor neuron degeneration. *J Biol Chem.* 2018;293:7606–17. PubMed PMID: 29599289.

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