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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 of copper transport caused by pathogenic variants in *ATP7A* (encoding a copper-transporting ATPase).

- Infants with classic Menkes disease appear healthy until age two to three months, when loss of developmental milestones, hypotonia, seizures, and failure to thrive occur. The diagnosis is usually suspected when infants exhibit typical neurologic changes and concomitant characteristic changes of the hair (short, sparse, coarse, twisted, and often lightly pigmented). Temperature instability and hypoglycemia may be present in the neonatal period. Death usually occurs 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.

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. The diagnosis of *ATP7A*-related copper transport disorders is most commonly

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established in a proband by detection of either a hemizygous *ATP7A* pathogenic variant in a male or a heterozygous *ATP7A* pathogenic variant in a female.

Management

Treatment of manifestations: Classic Menkes disease: gastrostomy tube placement to manage caloric intake; surgery for bladder diverticula.

Prevention of primary manifestations: Subcutaneous injections of copper histidine or copper chloride before age ten days normalizes developmental outcome in some children and improves the neurologic outcome in others.

Prevention of secondary complications: Antibiotic prophylaxis may prevent bladder infection.

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 will not be affected. Males with OHS or *ATP7A*-related DMN will pass the pathogenic variant to all of their daughters and none of their sons. Individuals with classic Menkes disease do not reproduce. When the 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 diagnosis are possible. Prenatal testing for Menkes disease is technically possible by copper transport studies in cultured chorionic villus cells or amniocytes, although its availability is limited.

GeneReview Scope

ATP7A-Related Copper Transport Disorders: Included Phenotypes
• 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

Menkes disease is suspected in males who develop hypotonia, failure to thrive, and seizures between age six and ten 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°), trichoclasis (transverse fracture of the hair shaft), and trichoptilosis (longitudinal splitting of the hair shaft). Because of the flattening of the normal cylindric structure, the periodicity of the twisting in *pili torti* is different from that found in naturally curly hair.

Specific clinical features include:

- Distinctive facial features: jowly appearance with sagging cheeks
- Pectus excavatum (midline depression in the bony thorax)
- Skin laxity, particularly on the nape of the neck and trunk
- Umbilical or inguinal hernias
- Hypotonia, neurodevelopmental delays, and failure to thrive, typically manifest by age three to six months

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

- 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 distal motor neuropathy resembling Charcot-Marie-Tooth disease, shares none of the clinical or biochemical abnormalities characteristic of Menkes disease or occipital horn syndrome, and is characterized by:

- Progressive distal motor neuropathy with minimal or no sensory symptoms
- Distal muscle weakness and atrophy in feet and hands with occasional *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. Serum Copper and Serum Ceruloplasmin Concentration in Males with Menkes Disease, Occipital Horn Syndrome, and *ATP7A*-Related Distal Motor Neuropathy

Serum Concentration	Menkes Disease [1]	OHS	*ATP7A*-Related DMN	Normal
Copper	0-55 µg/dL	40-80 µg/dL	80-100 µg/dL	70-150 µg/dL; (birth - 6 mos: 20-70 µg/dL)
Ceruloplasmin	10-160 mg/L	110-240 mg/L	240-310 mg/L	200-450 mg/L; (birth - 6 mos: 50-220 mg/L)

OHS = occipital horn syndrome
DMN = distal motor neuropathy
1. Diagnosis of Menkes disease using these studies alone in males under age six months is problematic given the normally low serum concentration in all children at this age.

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 variant in a male or a heterozygous *ATP7A* 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: 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.

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 and followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **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 at the most reasonable cost 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. Summary of Molecular Genetic Testing Used in *ATP7A*-Related Copper Transport Disorders

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method [3]
ATP7A	Sequence analysis [4, 5]	80%
	Gene-targeted deletion/duplication analysis [6]	20% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Tümer et al [2003]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.
5. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Culotta & Gitlin [2001]

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 Menkes disease and OHS (but normal in *ATP7A*-related DMN). Abnormal levels

reflect partial deficiency of dopamine beta hydroxylase (DBH), a copper-dependent enzyme critical for catecholamine biosynthesis

- **Copper transport studies in cultured fibroblasts.** Impaired cellular copper exodus is demonstrated by increased cellular copper retention in pulse-chase experiments with radiolabeled copper in cultured fibroblasts for Menkes disease.

  Note: This method is reserved for urgent prenatal testing when a family's *ATP7A* pathogenic variant is unknown; however, this situation should become exceedingly rare with increased availability 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 distal motor neuropathy (DMN). Classic Menkes disease is characterized by neurodegeneration and failure to thrive commencing at age two to three months. The age at diagnosis is usually about eight months. In contrast, OHS presents in early to middle childhood and is characterized predominantly by connective tissue abnormalities. *ATP7A*-related distal motor neuropathy is adult in onset, resembles Charcot-Marie-Tooth disease, and shares none of the clinical abnormalities characteristic of Menkes disease or OHS.

Classic Menkes disease. Infants appear healthy until age two to three months, when loss of 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.

Autonomic dysfunction including temperature instability and hypoglycemia may be present in the neonatal period; some infants have syncope and diarrhea.

Vascular tortuosity, bladder diverticula that can result in bladder outlet obstruction, and gastric polyps are common.

Without early treatment with parenteral copper, and sometimes even with such treatment, classic Menkes disease progresses to severe neurodegeneration and death between ages seven months and 3.5 years. Subdural hematomas and cerebrovascular accidents are common. Respiratory failure, often precipitated by pneumonia, is a common cause of death.

Imaging

- MRI shows defective myelination, atrophy with ventriculomegaly, and vascular tortuosity.
- MR angiography reveals a "corkscrew" appearance of cerebral vessels.
- Radiographs show Wormian bones and metaphyseal spurring and may show rib fractures.

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 talk. 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). Intelligence is normal or slightly reduced. The only apparent neurologic abnormalities of OHS are dysautonomia and subtle cognitive deficits. Affected individuals typically live to at least mid-adulthood. Fertility is unknown.

***ATP7A*-related distal motor neuropathy (DMN).** The age of onset ranges from five to 60 years, and is typically during the second or third decade of life [Kennerson et al 2010]. Findings include atrophy and weakness of distal muscles in hands and feet, foot drop with steppage gait, sometimes mild proximal weakness in the legs, with 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 orthotics 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 phenotype in Menkes disease, OHS, and *ATP7A*-related distal motor neuropathy (DMN) and with response to early copper treatment in Menkes disease [Kaler et al 2008].

Tümer et al [2003] observed that with rare exceptions gene deletions result in classic Menkes disease with death in early childhood.

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].

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 trichopoliodystrophy.

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

The incidence of Menkes disease and its variants is estimated at one in 100,000 births.

No estimates are available on the incidence of OHS and *ATP7A*-related DMN.

Genetically Related (Allelic) Disorders

Menkes disease, occipital horn syndrome, and *ATP7A*-related distal motor neuropathy are the only phenotypes currently known to be associated with pathogenic variants in *ATP7A*.

Differential Diagnosis

Menkes disease. The differential diagnosis includes other infantile-onset neurodevelopmental syndromes:

- Biotinidase deficiency
- Organic acidurias
- Aminoacidurias
- Mitochondrial myopathies (see Mitochondrial Disorders Overview)

Occipital horn syndrome. The differential diagnosis includes:

- *FBLN5*-related cutis laxa, inherited in an autosomal recessive or autosomal dominant manner (autosomal recessive inheritance is more common) and caused by mutation of *FBLN5* (encoding fibulin-5);
- *ELN*-related cutis laxa (OMIM 123700), inherited in an autosomal dominant manner and caused by mutation of *ELN* (encoding elastin).

***ATP7A*-related distal motor neuropathy.** The differential diagnosis includes other forms of Charcot-Marie-Tooth disease.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a male diagnosed with Menkes disease, the following evaluations are recommended:

- Developmental assessment
- Evaluation of feeding and nutrition
- Assessment of bladder function
- Consultation with a clinical geneticist and/or genetic counselor

To establish the extent of disease and needs in a male diagnosed with occipital horn syndrome (OHS), evaluations for the following are recommended:

- Bladder diverticula
- Inguinal hernias
- Vascular tortuosity
- Dysautonomia (chronic diarrhea, orthostatic hypotension). Note: Some medical centers have clinical autonomic testing laboratories.
- Mild cognitive deficits
- Consultation with a clinical geneticist and/or genetic counselor

To establish the extent of disease and needs in a male diagnosed with *ATP7A*-related distal motor neuropathy (DMN), the following evaluations are recommended:

- Neurologic examination
- EMG with nerve conduction studies
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Menkes disease

- Gastrostomy tube placement to manage caloric intake and general nutrition in some males with classic Menkes disease
- Surgery for bladder diverticula that occur in classic Menkes disease
- Developmental intervention

***ATP7A*-related DMN**

- Physical therapy (strength and stretching exercises)
- Occupational therapy
- Ankle foot orthotics

Prevention of Primary Manifestations

Menkes disease. In classic Menkes disease, treatment with subcutaneous injections of copper histidine or copper chloride before age ten days normalizes developmental outcome in some individuals and improves the neurologic outcome in others [Kaler et al 2008, Kaler et al 2010].

Note: Despite very early copper histidine treatment, some infants show no significant improvement relative to the natural history of untreated Menkes disease [Kaler et al 1995, Kaler et al 2008]. The type and severity of the *ATP7A* pathogenic variant determine the response to early copper treatment.

To maintain serum copper concentration in the normal range (70-150 µg/dL), the suggested dose of copper chloride is:

- For children age <1 year: 250 µg administered subcutaneously 2x/day
- For children age >1 year: 250 µg administered subcutaneously 1x/day

Occipital horn syndrome. Although there is no evidence that copper replacement therapy for OHS is clinically beneficial, it would be reasonable to expect even better overall neurodevelopmental and neurocognitive outcomes if individuals with OHS were identified early and treated with copper during their first three years.

Prevention of Secondary Complications

Antibiotic prophylaxis may be necessary to prevent bladder infection.

Surveillance

For infants being treated with copper histidine or copper chloride, monitor serum copper and ceruloplasmin levels to avoid supranormal levels.

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

Adeno-associated viral gene therapy in a mouse model is under active investigation with promising early results [Donsante et al 2011].

Newborn screening is not currently available for Menkes disease because biochemical strategies are not practical with current newborn screening platforms. A pilot study to evaluate the potential of sequence analysis of *ATP7A* from dried blood spots is currently in progress. If successful, such testing would allow early diagnosis and treatment.

Search ClinicalTrials.gov in the US and www.ClinicalTrialsRegister.eu 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Menkes disease, occipital horn syndrome, and *ATP7A*-related distal motor neuropathy are inherited in an X-linked manner.

Risk to Family Members

Parents of a 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.
- 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 son and no other affected relatives and if the *ATP7A* pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novoATP7A* pathogenic variant, in which case the mother is not a carrier. About one third of affected males represent simplex cases.

Sibs of a 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 transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and usually will not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *ATP7A* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a proband

- Males with OHS and *ATP7A*-related DMN pass the pathogenic variant to all of their daughters and none of their sons.
- To date males with classic Menkes disease have not reproduced.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the pathogenic variant and the aunts' offspring, depending on their gender, may be at risk of being heterozygotes (carriers) for the *ATP7A* pathogenic variant or of being affected.

Heterozygote (Carrier) Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *ATP7A* pathogenic variant has been identified in an affected relative.

Note: Identification of heterozygous females requires either (a) prior identification of the *ATP7A* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and then, if a pathogenic variant is not identified, by gene-targeted deletion/duplication analysis.

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, clarification of genetic status, and discussion of the availability of prenatal 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 being affected.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *ATP7A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

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.

- **Medline Plus**
  Menkes syndrome
- **My46 Trait Profile**
  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

- **National Library of Medicine Genetics Home Reference**
  Menkes syndrome
- **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
ATP7A	Xq21.1	Copper-transporting ATPase 1	ATP7A @ LOVD	ATP7A	ATP7A

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)

300011	ATPase, Cu(2+)-TRANSPORTING, ALPHA POLYPEPTIDE; ATP7A
300489	SPINAL MUSCULAR ATROPHY, DISTAL, X-LINKED 3; SMAX3
304150	OCCIPITAL HORN SYNDROME; OHS
309400	MENKES DISEASE; MNK

Gene structure. *ATP7A* contains 23 exons spanning 150 kb of genomic DNA. The coding sequence is 4.5 kb. Rarely, alternatively spliced transcripts (of uncertain significance) are discerned in normal tissues. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants tend to be family specific (unique). Variant types include: small insertions and deletions (35%); nonsense (20%), splicing (15%), and missense (8%) variants; and large deletions or rearrangements (20%) [Culotta & Gitlin 2001].

ATP7A-related distal motor neuropathy involves 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.

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

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

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Chapter Notes

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