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TUBB4A-Related Leukodystrophy

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Summary

Clinical characteristics

TUBB4A-related leukodystrophy comprises a phenotypic spectrum in which the MRI findings range from hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) at the severe end to isolated hypomyelination at the mild end. Progressive neurologic findings reflect involvement of the pyramidal tracts (spasticity, brisk deep tendon reflexes, and Babinski sign), extrapyramidal system (rigidity, dystonia, choreoathetosis, oculogyric crisis, and perioral dyskinesia), cerebellum (ataxia, intention tremor, dysmetria), and bulbar function (dysarthria, dysphonia, and swallowing). Cognition is variably affected, usually less severely than motor function. Typically, those with H-ABC present in early childhood (ages 1-3 years) and those with isolated hypomyelination in later childhood or adulthood. The rate of progression varies with disease severity.

Diagnosis/testing

The diagnosis is established in a proband with characteristic clinical and MRI findings and a heterozygous *TUBB4A* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Functionally disabling spasticity requires medical management and physical therapy; dystonia requires medical management and – when refractory to medical management – possibly surgical intervention. Swallowing dysfunction may require use of a gastrostomy tube for feeding. Seizures, constipation, and gastroesophageal reflux disease are treated in the routine manner.

Prevention of secondary complications: Calcium and vitamin D supplementation as required to prevent osteoporosis; attention to skin care and frequent repositioning to help prevent pressure sores in individuals with decreased mobility; annual flu vaccination; use of routine fall prevention strategies, adaptive equipment (e.g., wheelchairs and walkers), and physical therapy to help prevent secondary injury.

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Surveillance: Routine evaluations of (1) swallowing and feeding to reduce the risk of aspiration; (2) nutrition to prevent malnutrition; (3) orthopedic and joint integrity to detect joint dislocation and scoliosis. At least yearly: (1) medical evaluations to assess weight and medications; (2) evaluations by specialists in occupational therapy, physical therapy, speech therapy, rehabilitation medicine. Annual neurologic assessment to detect emerging complications.

Genetic counseling

TUBB4A-related leukodystrophy is inherited in an autosomal dominant manner. Most affected individuals have the disorder as the result of a *de novo* pathogenic variant. The risk to sibs of a proband with clinically unaffected parents is low but greater than that of the general population because of the possibility of germline mosaicism or somatic and germline mosaicism in a parent. Individuals with *TUBB4A*-related leukodystrophy are not known to reproduce.

GeneReview Scope

TUBB4A-Related Leukodystrophy: Included Phenotypes [1]
• Hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC) • Isolated hypomyelination

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

TUBB4A-related leukodystrophy **should be suspected** in individuals with the following clinical and brain MRI findings that define the two hypomyelination phenotypes.

Clinical findings

- Onset during infancy or childhood
- Motor developmental delay
- Presence of pyramidal and extrapyramidal signs
- Gait ataxia and cerebellar dysfunction
- Dysarthria, aphonia, or "whispering" dysphonia

Brain MRI findings

- **Hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC)** [van der Knaap et al 2002, Sasaki et al 2009, Blumkin et al 2014, Ferreira et al 2014, Hamilton et al 2014, Sagnelli et al 2016, Tonduti et al 2016] is characterized by (Figure 1):
  - Progressive atrophy of the basal ganglia involving the neostriatum (i.e., the putamen and caudate nucleus) predominantly, often with a significant decrease in size of the putamen (which can disappear over time) and to a lesser degree the head of the caudate. The thalamus and globus pallidus are typically spared. Note that although changes in the putamen are evident in many children with the H-ABC phenotype by age two years, in some children the changes may not be evident until later childhood.
  - Diffuse cerebral hypomyelination manifest as mild T_2-weighted hyperintensity involving the supratentorial white matter, corpus callosum, and internal capsule, and typically isointense or mildly hyperintense T_1-weighted signal

- Cerebellar findings of white matter T_1-weighted signal that is isointense or mildly hyper- or hypointense relative to gray matter structures. Cerebellar atrophy prominently affecting the vermis is a common but not obligatory feature of H-ABC.

- ***TUBB4A*-related isolated hypomyelination** is characterized by variable cerebellar involvement and no evident neostriatal involvement [Pizzino et al 2014, Purnell et al 2014].

Establishing the Diagnosis

The diagnosis of a *TUBB4A*-related leukodystrophy **is established** in a proband with characteristic clinical and MRI findings and a heterozygous *TUBB4A* pathogenic variant identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel or single-gene testing) and **genomic testing** (comprehensive genomic sequencing) depending on the phenotype.

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Because the phenotype of *TUBB4A*-related leukodystrophy is broad, children with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a mild phenotype indistinguishable from many other inherited hypomyelinating leukodystrophies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1. Gene-Targeted Testing

When the phenotypic findings, such as hypomyelination with basal ganglia atrophy, suggest the diagnosis of *TUBB4A*-related leukodystrophy, molecular genetic testing approaches can include the following:

- **Recommended: single-gene testing.** Sequence analysis of *TUBB4A* is performed first. If only one pathogenic variant is found, gene-targeted deletion/duplication analysis could be considered; however, to date no exon or whole-gene deletions have been reported.

- **To consider: multigene panel.** A multigene leukodystrophy panel that includes *TUBB4A* and other genes of interest (see Differential Diagnosis) may be considered; however, the diagnostic sensitivity of a multigene panel may be low in this instance because primary neuronal disorders with MRI findings that resemble a classic leukodystrophy (like *TUBB4A*-related leukodystrophy) are often not included in leukodystrophy panels.

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

Option 2. Genomic Testing

When the phenotype is indistinguishable from many other inherited disorders with leukodystrophy or with atypical white matter changes on MRI, **comprehensive genomic testing,** which does not require the clinician to determine which gene(s) are likely involved, may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

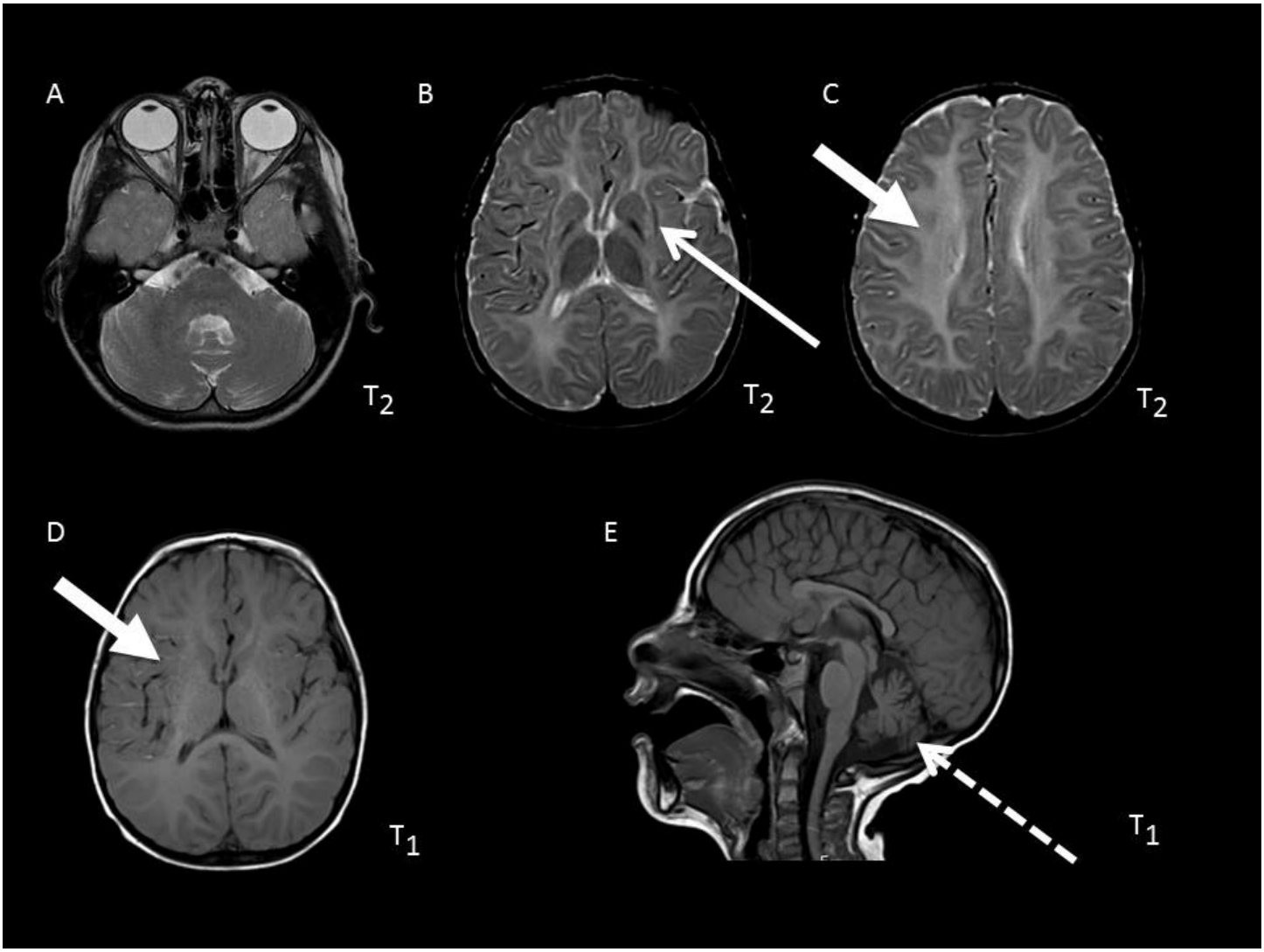

Figure 1. MRI findings

A. Cerebellar white matter T_1-weighted signal that is isointense or mildly hyper- or hypointense relative to gray matter structures; cerebellar atrophy prominently affects the vermis. There are no specific signal changes to the brain stem or dentate nucleus that could help differentiate *TUBB4A*-related leukodystrophy from other hypomyelinating leukodystrophies.

B. Progressive atrophy of the basal ganglia predominantly involving the neostriatum (i.e., the putamen and caudate nucleus), often with a significant decrease in size of the putamen (thin white arrow) and to a lesser degree the head of the caudate. The thalamus and globus pallidus are typically spared.

C. Diffuse cerebral hypomyelination manifesting as mild T_2-weighted hyperintensity involving the supratentorial white matter (thick white arrow)

D. Diffuse cerebral hypomyelination typically manifesting as isointense or mild T_1-weighted hyperintensity involving the supratentorial white matter (thick white arrow)

E. Cerebellar white matter T_1-weighted signal that is isointense or mildly hyper- or hypointense relative to gray matter structures. Although cerebellar atrophy prominently affecting the vermis is common (dotted line arrow), it is not an obligatory finding.

Table 1. Molecular Genetic Testing Used in *TUBB4A*-Related Leukodystrophy

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TUBB4A	Sequence analysis [3]	71/71 affected persons
	Gene-targeted duplication/deletion analysis [4]	None reported

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. 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. 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.

Clinical Characteristics

Clinical Description

TUBB4A-related leukodystrophy typically presents between ages one and three years; onset range is a few months of age in more severe forms [van der Knaap et al 2002] to later childhood or adulthood in some instances of isolated hypomyelination [Hamilton et al 2014, Pizzino et al 2014, Shimojima et al 2015].

The disorder is progressive; rate of progression varies with disease severity. Males and females are similarly affected.

Manifestations can include the following.

Delayed motor development. Some children have a period of normal motor development with subsequent deterioration [van der Knaap et al 2002].

Cognitive dysfunction. Cognition is variably affected but usually less severely than motor function. Learning difficulty is common; social awareness is usually preserved.

Pyramidal involvement. Bilateral or unilateral upper-motor neuron dysfunction (spasticity, brisk deep tendon reflexes, and Babinski signs) typically manifests in early childhood [Mercimek-Mahmutoglu et al 2005, Wakusawa et al 2006].

Of note, some individuals with a heterozygous *TUBB4A* pathogenic variant and a spastic paraplegia have been described as having mild white matter changes on brain MRI [Kancheva et al 2015], thus expanding the spectrum of *TUBB4A*-related leukodystrophy. To date, however, molecular genetic testing of individuals with as-yet unclassified hereditary spastic paraplegia has not commonly identified a causative heterozygous *TUBB4A* pathogenic variant [Kumar et al 2015].

Extrapyramidal involvement due to neostriatal involvement includes rigidity, dystonia, choreoathetosis, oculogyric crisis, and perioral dyskinesia. Extrapyramidal features – in particular hemidystonia – can be the first manifestation of this condition. Extrapyramidal features can be exacerbated by changes in body position or by visual and acoustic stimuli.

Gait dysfunction. Although some individuals achieve independent ambulation, many never do. Gait instability and falls are common.

Cerebellar signs can include ataxia, intention tremor, dysmetria, and nystagmus.

Dysarthria, dysphonia, and swallowing dysfunction. Communication and feeding difficulties emerge over time, necessitating a gastrostomy tube for feeding in many individuals.

Other less common findings (seen in severe cases) can include the following [van der Knaap et al 2002, Sasaki et al 2009, Simons et al 2013, Ferreira et al 2014, Hamilton et al 2014]:

- Microcephaly
- Short stature
- Seizures
- Poor vision
- Hearing loss
- Scoliosis and joint dislocation resulting from a combination of motor dysfunction and improper positioning
- Hypogonadotropic hypogonadism (in 1 individual) [Tonduti et al 2016]

Individuals mosaic for a *TUBB4A* pathogenic variant. Of note, a few parents of individuals with *TUBB4A*-related hypomyelination have been asymptomatic and mosaic for a *TUBB4A* pathogenic variant [Simons et al 2013].

Neurophysiologic studies

- Electroencephalogram is usually normal or demonstrates slow background activity.
- Electromyogram and nerve conduction studies are normal.
- Brain stem evoked potentials are usually delayed.
- Visual evoked potentials are usually normal.
- Somatosensory evoked potentials in some instances show delayed conduction [van der Knaap et al 2002].

Laboratory findings. Cerebrospinal fluid (CSF) analysis is typically normal [van der Knaap et al 2002]. Of note, in some individuals a low level of CSF 5-methyltetrahydrofolic acid was observed with normal plasma folate levels and normal CSF 5-MTHF reductase or decreased CSF homovanillic acid [Tomás-Vila et al 2014, Tonduti et al 2016]; this has not been broadly described [Mercimek-Mahmutoglu & Stockler-Ipsiroglu 2007] and thus is not thought to be a primary metabolic defect.

Genotype-Phenotype Correlations

Four *TUBB4A* pathogenic variants are consistently associated with specific phenotypes:

- c.745G>A. In the initial study of persons with classic H-ABC MRI findings, all had this *TUBB4A* pathogenic variant [Simons et al 2013]. Subsequently, individuals with the classic H-ABC phenotype (Table 2) were found to have this pathogenic variant as well as others [Hamilton et al 2015].
- c.730G>A. Individuals with this pathogenic variant have a typical H-ABC phenotype, but with more severe lack of myelin and a more rapidly progressive disease course [Carvalho et al 2015].
- c.785G>A and c.1228G>A. These pathogenic variants have been described in several individuals with hypomyelination without atrophy of the basal ganglia [Ferreira et al 2014, Hamilton et al 2014, Miyatake et al 2014].

Penetrance

The penetrance is not known but appears to be 100%.

Of note, a few parents of individuals with *TUBB4A*-related hypomyelination have been asymptomatic and mosaic for a *TUBB4A* pathogenic variant [Simons et al 2013].

Prevalence

The exact prevalence is unknown; 71 affected individuals have been reported to date.

Genetically Related (Allelic) Disorders

In addition to the leukodystrophies caused by a heterozygous *TUBB4A* pathogenic variant described in this *GeneReview*, the *TUBB4A* pathogenic variant c.4C>G causes the adult-onset disorder laryngeal dysphonia or whispering dysphonia (also known as DYT4 dystonia), in which brain MRI is normal. Affected individuals develop generalized dystonia and ataxic gait later in the disease course [Hersheson et al 2013]. Swallowing difficulty is sometimes observed.

While Erro et al have hypothesized that the two *TUBB4A*-related leukodystrophy phenotypes (H-ABC and isolated hypomyelination) and DYT4 represent a spectrum of *TUBB4A*-related disorders, DYT4 dystonia differs from the leukodystrophies in that a positive family history with autosomal dominant inheritance is typical [Erro et al 2015a, Erro et al 2015b].

Differential Diagnosis

Hypomyelinating leukodystrophies with early childhood onset and/or extrapyramidal signs should be considered in the differential diagnosis.

Pelizaeus-Merzbacher disease (PMD) is an X-linked disorder caused by a *PLP1* intragenic pathogenic variant or a large *PLP1* deletion/duplication. It typically presents during infancy or early childhood with a combination of nystagmus, upper motor neuron dysfunction, gait ataxia, and extrapyramidal signs. Brain MRI shows diffuse hypomyelination but lacks the classic atrophy of the cerebellum and basal ganglia of a *TUBB4A*-related leukodystrophy, hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC).

Pelizaeus-Merzbacher-like disease 1 (PMLD1) is an autosomal recessive disorder caused by biallelic *GJC2* pathogenic variants. PMLD1 usually presents during early childhood with manifestations similar to those of the H-ABC phenotype including: developmental delay, speech delay, pyramidal and extrapyramidal involvement, cerebellar signs, and preservation of mental functions. Much like those with PMD, affected children manifest nystagmus early in the disease course [Uhlenberg et al 2004], which – although it is described in *TUBB4A*-related leukodystrophy – is not typical.

Pol III-related leukodystrophies are autosomal recessive disorders caused by biallelic pathogenic variants in one of three genes (*POLR3A*, *POLR3B*, or *POLR1C*). Manifestations include spasticity, gait ataxia, extrapyramidal movement disorders, and cerebellar signs, similar to those of *TUBB4A*-related leukodystrophy. Other manifestations of Pol III-related leukodystrophies include abnormal dentition and hypogonadotropic hypogonadism, which are not commonly associated with *TUBB4A*-related leukodystrophy.

***SOX 10*-associated leukodystrophy/peripheral and central demyelination, Waardenburg syndrome, and Hirschsprung disease (PCWH)** (OMIM 609136) is an autosomal dominant disorder caused by heterozygous pathogenic variants in *SOX10*. Manifestations overlap with *TUBB4A*-related leukodystrophy, including developmental delay, spasticity, gait ataxia, and extrapyramidal movement disorders. Additional manifestations of PCWH include:

- Involvement of the peripheral nervous system (sensory loss)
- Waardenburg syndrome (skin and hair pigmentation changes, heterochromia iridis, and hearing loss) and Hirschsprung disease [Inoue et al 2002, Bondurand et al 2007]

Free sialic acid storage disorders are autosomal recessive neurodegenerative disorders caused by biallelic pathogenic variants in *SLC17A5* that result in defective sialic acid storage and transport. Whereas the most severe form (infantile free sialic acid storage disease) includes coarse facial features and non-neurologic manifestations such as hepatosplenomegaly and cardiomegaly, the milder form (Salla disease) is similar to H-ABC and includes progressive neurologic deterioration with spasticity, extrapyramidal movement disorders, and seizures.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *TUBB4A*-related leukodystrophy, the following evaluations are recommended [Van Haren et al 2015]:

- Evaluation by a pediatric neurologist for evidence of developmental delay, spasticity, and extrapyramidal movement disorders
- Assessment of developmental milestones and cognitive function
- Assessment of functional disability and equipment needs by a physiotherapist
- Assessment of speech (communication) and feeding (swallowing)
- Audiologic assessment
- Orthopedic evaluation for evidence of scoliosis and/or joint deformity, particularly in individuals with significant dystonia
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Although there is no curative treatment for *TUBB4A*-related leukodystrophies, quality of life can be improved in the following ways.

- Spasticity that is functionally disabling can lead to joint contractures and scoliosis; both require physical therapy (stretching and positioning) and medical management. Oral GABA agonists such as baclofen and diazepam can be used. In some instances intrathecal baclofen pumps can be considered. For focal spasticity, intramuscular botulinum toxin may be helpful.
- Dystonia can be managed with:
  - Baclofen or intramuscular botulinum toxin when associated with spasticity;
  - Trihexyphenidyl or tetrabenazine;
  - High doses of levodopa and carbidopa [Wakusawa et al 2006, Tonduti et al 2016].
- When dystonia is refractory to medical management, a baclofen pump may be considered. Of note, to date deep brain stimulation has not been studied in *TUBB4A*-related leukodystrophy.
- Swallowing dysfunction may result in use of a gastrostomy tube for feeding to reduce the risk of aspiration.
- Dysarthria may warrant augmentative communication tools.
- Anticonvulsant medications should be used when seizures are present.
- Constipation, commonly due to neurologic dysfunction and poor intestinal motility, can be treated with diet, laxatives, and stool softeners.
- Gastroesophageal reflux disease is common and should be considered in the evaluation of pain.
- Functional ability can be improved by use of walkers or wheeled mobility devices and other necessary equipment.
- Accommodations in school such as an individual educational plan are often needed. With such accommodations many children with the classic H-ABC phenotype perform at or near grade level for many years, although cognitive decline may be seen later.

- Family support and advocacy groups can provide needed psychosocial support for affected individuals.

Prevention of Secondary Complications

The following recommendations – based on consensus – have been developed for all leukodystrophies [Van Haren et al 2015].

- Calcium and vitamin D supplementation as required to prevent osteoporosis
- Skin care and frequent repositioning to help prevent pressure sores in individuals with decreased mobility
- Annual flu vaccination
- Fall prevention strategies, adaptive equipment (e.g., wheelchairs and walkers), and physical therapy (to increase strength) to help prevent secondary injury

Surveillance

The following are appropriate:

- Routine evaluations of swallowing and feeding to reduce the risk of aspiration, and nutrition to prevent malnutrition
- At least yearly:
  - Medical evaluation including physical examination to assess weight and medications
  - Evaluations by specialists in occupational therapy, physical therapy, speech therapy, and rehabilitation medicine
  - Evaluation by orthopedists to assess for scoliosis and joint dislocation
- Annual neurologic evaluation to assess symptoms and any emerging complications

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search 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. Note: There may not be clinical trials for this disorder.

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

TUBB4A-related leukodystrophy is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most probands with *TUBB4A*-related leukodystrophy have the disorder as the result of a *de novo* pathogenic variant.

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing.
- If the *TUBB4A* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or mosaicism in a parent [Simons et al 2013].
- If the parent is the individual in whom the *TUBB4A* pathogenic variant first occurred, he or she may have germline mosaicism or somatic and germline mosaicism for the variant and be asymptomatic [Simons et al 2013].

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- Because *TUBB4A*-related leukodystrophy has occurred as the result of a *de novo* pathogenic variant in most cases reported to date, the risk to the sibs of a proband is presumed to be low but greater than that of the general population because of the possibility of germline mosaicism or somatic and germline mosaicism in a parent.

  Sib recurrence was reported in a family in which the asymptomatic mother was found to be mosaic for a *TUBB4A* pathogenic variant [Simons et al 2013].

Offspring of a proband. Each child of an individual with *TUBB4A*-related leukodystrophy would have a 50% chance of inheriting the *TUBB4A* pathogenic variant; however, individuals with *TUBB4A*-related leukodystrophy are not known to reproduce.

Other family members. Given that most probands with *TUBB4A*-related leukodystrophy reported to date have the disorder as a result of a *de novo TUBB4A* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TUBB4A* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing 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.

- **European Leukodystrophy Association (ELA)**
  Phone: 03 83 30 93 34
  www.ela-asso.com
- **Leukodystrophy Australia**

Australia
Phone: 1800-141-400
Email: info@leuko.org.au
www.leuko.org.au

- **Medical Home Portal**
  Leukodystrophies
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  www.ulf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

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. TUBB4A-Related Leukodystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
TUBB4A	19p13.3	Tubulin beta-4A chain	TUBB4A	TUBB4A

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 TUBB4A-Related Leukodystrophy (View All in OMIM)

602662	TUBULIN, BETA-4A; TUBB4A
612438	LEUKODYSTROPHY, HYPOMYELINATING, 6; HLD6

Gene structure. Alternate splicing results in multiple transcript variants that encode different isoforms (see Table A, **Gene** for details). The transcript variant NM_006087.3 is 2583 bp and comprises four exons [Lee et al 1984].

Pathogenic variants. See Table 2 and Table 3 (pdf) for a listing of pathogenic variants.

Variant c.745G>A is the most common *TUBB4A* pathogenic variant; it is consistently associated with the classic phenotype of hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC).

Variant c.4C>G is not associated with a leukodystrophy but with DYT4 ("hereditary whispering dysphonia") [Hersheson et al 2013].

Table 2. *TUBB4A* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.4C>G [1]	p.Arg2Gly	NM_006087.3 NP_006078.2
c.730G>A [2, 3]	p.Gly244Ser	
c.745G>A [2, 3, 4, 5]	p.Asp249Asn	
c.785G>A [2, 3, 4]	p.Arg262His	
c.1228G>A [2, 4]	p.Glu410Lys	

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). See Quick Reference for an explanation of nomenclature.
1. Hersheson et al [2013]
2. See Genotype-Phenotype Correlations.
3. Hamilton et al [2014]
4. Miyatake et al [2014]
5. Simons et al [2013], Ferreira et al [2014]

To view information on additional variants, see Table 3 (pdf).

Normal gene product. The transcript variant NM_006087.3 encodes a β-tubulin protein isoform of 444 amino acids. β-tubulin proteins can bind to α-tubulins to form heterodimers, which form copolymers that assemble into microtubules. Microtubules are an essential component of the cytoskeleton and play important roles in many cellular processes such as mitosis, motility, and transport.

TUBB4A is predominantly expressed in the CNS, especially in the cerebellum and putamen and white matter [Nogales 2001, Hersheson et al 2013].

Abnormal gene product. Pathogenic variants in *TUBB4A* result in changes in β-tubulin structure that are thought to affect microtubule polymerization or stability [Savage et al 1994].

Chapter Notes

Revision History

- 3 November 2016 (bp) Review posted live
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