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LMNB1-Related Autosomal Dominant Leukodystrophy

Synonyms: Adult-Onset Autosomal Dominant Leukodystrophy with Autonomic Symptoms, Autosomal Dominant Adult-Onset Demyelinating Leukodystrophy, Autosomal Dominant Leukodystrophy with Autonomic Symptoms, *LMNB1*-Related ADLD

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Summary

Clinical characteristics

LMNB1-related autosomal dominant leukodystrophy (ADLD) is a slowly progressive disorder of central nervous system white matter characterized by onset of autonomic dysfunction in the fourth to fifth decade, followed by pyramidal and cerebellar abnormalities resulting in spasticity, ataxia, and tremor. Autonomic dysfunction can include bladder dysfunction, constipation, postural hypotension, erectile dysfunction, and (less often) impaired sweating. Pyramidal signs are often more prominent in the lower extremities (e.g., spastic weakness, hypertonia, clonus, brisk deep tendon reflexes, and bilateral Babinski signs). Cerebellar signs typically appear at the same time as the pyramidal signs and include gait ataxia, dysdiadochokinesia, intention tremor, dysmetria, and nystagmus. Many individuals have sensory deficits starting in the lower limbs. Pseudobulbar palsy with dysarthria, dysphagia, and forced crying and laughing may appear in the seventh or eighth decade. Although cognitive function is usually preserved or only mildly impaired early in the disease course, dementia and psychiatric manifestations can occur as late manifestations. Affected individuals may survive for decades after onset.

Diagnosis/testing

The diagnosis of *LMNB1*-related ADLD is established in a proband with suggestive clinical and MRI findings and either an *LMNB1* duplication or (more rarely) a heterozygous deletion upstream of the *LMNB1* promoter identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic. For autonomic dysfunction:

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- Neurogenic bladder may require management of urinary retention and/or urgency and recurrent urinary tract infection.
- Constipation may require good hydration, increased dietary fiber, stool softeners, and/or laxatives.
- Orthostatic hypotension can be minimized by pharmacologic intervention, compression stockings, physical therapy, and increased dietary salt.
- Erectile dysfunction is treated medically.
- Impaired sweating is managed with cool environment and attention to fever during infection.

Spasticity may be treated with medications and physical therapy. Ataxia can be managed with strategies to minimize falls and increase strength, and adaptive equipment such as walkers or wheelchairs. Feeding difficulties can be managed with speech therapy and appropriate feeding interventions to assure adequate nutrition while preventing aspiration pneumonia.

Surveillance: Routine assessment of: weight, nutrition, and feeding; pulmonary status (re possible recurrent pneumonia); bladder and erectile function; psychosocial well-being; and medications/doses to avoid iatrogenic polypharmacy. At least yearly assessment: by a neurologist for disease manifestations and progression; and by a physiatrist, orthopedist, physical therapist, and occupational therapist to address orthopedic, equipment, and functional needs.

Genetic counseling

LMNB1-related ADLD is inherited in an autosomal dominant manner. To date, all individuals diagnosed with *LMNB1*-related ADLD whose parents have undergone molecular genetic testing have the disorder as the result of a large *LMNB1* duplication (or a deletion upstream of *LMNB1)* inherited from an affected parent. Each child of an individual with *LMNB1*-related ADLD has a 50% chance of inheriting the *LMNB1* duplication (or deletion upstream of *LMNB1*). Once the causative pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *LMNB1*-related ADLD are possible.

Diagnosis

No formal diagnostic criteria exist.

Suggestive Findings

LMNB1-related autosomal dominant leukodystrophy (ADLD) **should be suspected** in adults with the following clinical, neuroimaging, and family history findings:

Clinical features

- Onset in the fourth to fifth decade of signs and symptoms of autonomic dysfunction including bladder dysfunction, constipation, erectile dysfunction, and postural hypotension
- Subsequent onset of motor and cerebellar impairment resulting in spasticity, ataxia, and tremor

MRI findings. Brain and spinal cord MRI findings can precede clinical manifestations by decades.

Specific brain and spine MRI findings suggestive of *LMNB1*-related ADLD [Bergui et al 1997, Melberg et al 2006, Sundblom et al 2009, Finnsson et al 2015)] include the following:

- Symmetric T_2-weighted hyperintensities in the cerebral white matter extending from below the motor cortex, following corticospinal tracts downward through the posterior limb of the internal capsule toward the pyramids in the medulla oblongata. Over time, the signal abnormalities extend around the lateral ventricles from the frontal lobe to the parietal and occipital lobes and finally the temporal lobe to become completely confluent (Figure 1).

- Periventricular rims around the lateral ventricles are spared or mildly affected.
- Early involvement of the upper and middle cerebellar peduncles with marked T_2-weighted hyperintensity (Figure 1 A). The middle cerebellar peduncles may be spared in some individuals.
- Atrophy of the spinal cord is common, often with an increased T_2-weighted signal intensity in the entire spinal cord white matter (Figure 2).
- Brain atrophy may develop over time.
- No pathologic enhancement is seen after contrast medium administration.

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *LMNB1*-related ADLD **is established** in a proband with suggestive clinical and MRI findings and either an *LMNB1* duplication or (more rarely) a heterozygous deletion upstream of the *LMNB1* promoter identified on molecular genetic testing [Giorgio et al 2015] (see Table 1).

Note: Identification of a heterozygous *LMNB1* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

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

- **Single-gene testing.** Gene-targeted duplication/deletion analysis of *LMNB1* (including the region upstream of the LMNB1 promoter) should be performed in individuals with classic clinical and neuroimaging features of *LMNB1*-related ADLD.
- **A multigene panel** that includes *LMNB1* and other genes of interest (see Differential Diagnosis) 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.

  Note: (1) **Attention should be given to whether the panel includes duplication/deletion analysis**, as sequence variants of *LMNB1* are not known to be associated with *LMNB1*-related ADLD. (2) 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. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) 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. (5) 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.

Comprehensive genomic testing including **exome sequencing** and **genome sequencing** is not recommended for *LMNB1*-related ADLD as this type of testing is not typically able to detect the duplication or upstream deletion of *LMNB1* associated with this disorder.

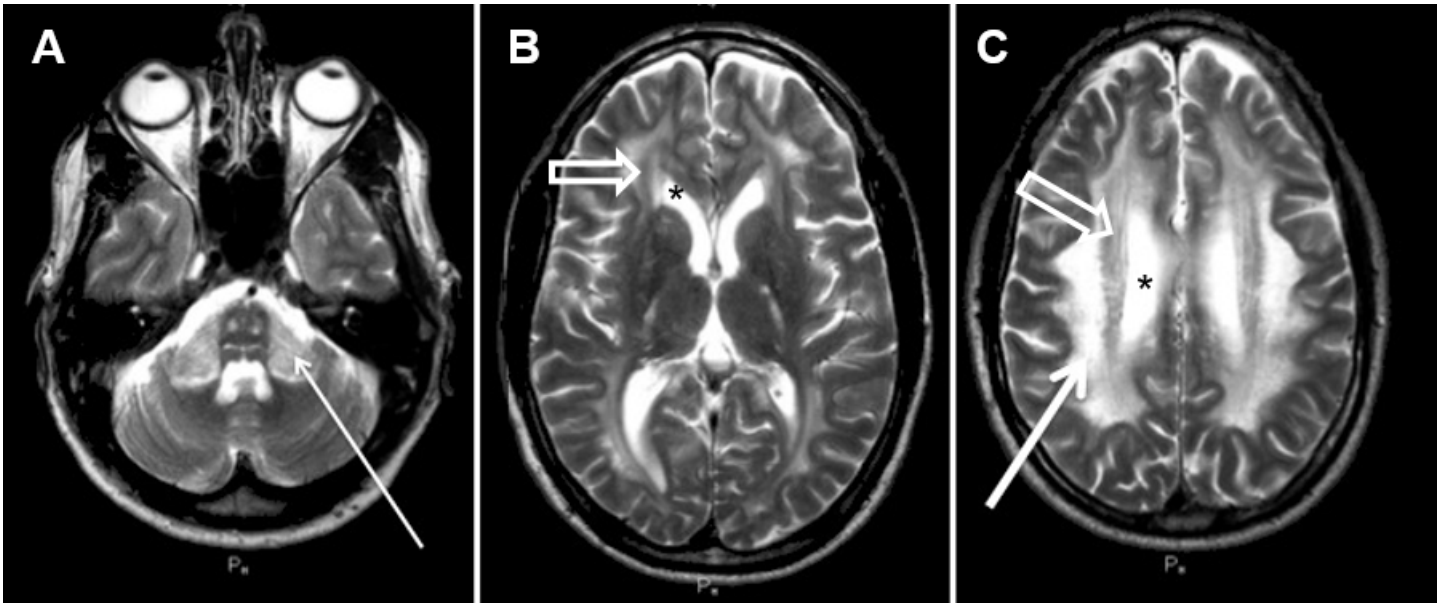

Figure 1. T_2-weighted spin echo MR images from a male age 55 years with *LMNB1*-related ADLD with autonomic symptoms. Axial slices at the levels of the pons (A), the III ventricle (B) and the upper lateral ventricles (C). The middle cerebellar peduncles are involved (A, thin arrow). Corticospinal tract involvement is seen as hyperintensities both in the pons (A) and in the posterior limbs of the internal capsules (B). Extensive supratentorial white matter changes are seen in B and C (thick arrow). Less affected periventricular rims (B and C, open arrows) are characteristic for *LMNBI*-related ADLD.

* lateral ventricle

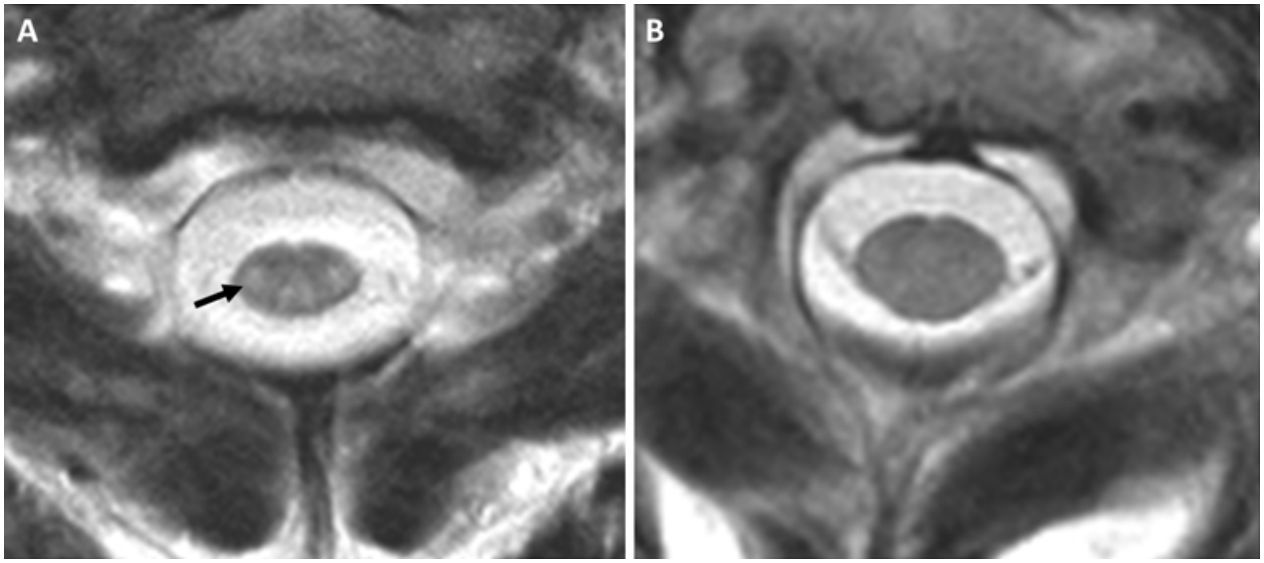

Figure 2. Transverse T_2-weighted spin echo MR images at the level of C II of an individual with *LMNB1*-related ADLD (A) and a healthy control (B). In the affected individual, the cross-sectional area of the spinal cord is reduced and the signal intensity of white matter is increased (black arrow).

Table 1. Molecular Genetic Testing Used in *LMNB1*-Related Autosomal Dominant Leukodystrophy (ADLD)

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
LMNB1	Gene-targeted deletion/ duplication analysis [3, 4]	• *LMNB1* duplication in 28/33 published families [5] • A heterozygous deletion upstream of the *LMNB1* promoter in 5/33 published families [6]

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. 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.
4. To include analysis upstream of the *LMNB1* promoter
5. Padiath et al [2006], Giorgio et al [2013], Potic et al [2013], Dai et al [2017], Mezaki et al [2018], Zhang et al [2019]
6. Giorgio et al [2015], Mezaki et al [2018], Nmezi et al [2019]

Clinical Characteristics

Clinical Description

LMNB1-related autosomal dominant leukodystrophy (ADLD) is a slowly progressive neurologic disorder of central nervous system white matter. Adults show autonomic dysfunction, the first evidence of the disorder, in the fourth to fifth decade of life, followed by pyramidal and cerebellar abnormalities resulting in spasticity, ataxia, and tremor [Finnsson et al 2015].

To date, at least 33 families have been identified with a pathogenic variant in *LMNB1* [Eldridge et al 1984, Quattrocolo et al 1997, Coffeen et al 2000, Marklund et al 2006, Padiath et al 2006, Meijer et al 2008, Brussino et al 2009, Schuster et al 2011, Dos Santos et al 2012, Molloy et al 2012, Potic et al 2013, Dai et al 2017, Sandoval-Rodríguez et al 2017, Mezaki et al 2018, Zhang et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Autonomic dysfunction, a nearly universal feature [Padiath & Fu 2010], includes bladder dysfunction, constipation, postural hypotension, erectile dysfunction, and (less often) impaired sweating. Symptoms of autonomic dysfunction may be the initial disease presentation and can precede the motor and cerebellar manifestations by months to years.

- Neurogenic bladder is commonly complicated by urinary urgency and/or incomplete bladder emptying, which is often complicated by urinary tract infection.
- Orthostatic hypotension can be asymptomatic or symptomatic (frequent fainting results in significant functional disability) [Finnsson et al 2015].
- Temperature dysregulation and heat intolerance can be a common feature in individuals with *LMNB1*-related ADLD [Finnsson et al 2015]. In rare cases hypothermia can be severe and life threatening [Meijer et al 2008]. Infection may exacerbate temperature instability; for example, body temperature decreased to 29.5° C in one individual with pneumonia [Finnsson et al 2015].
- It has been hypothesized that spinal cord white matter involvement [Finnsson et al 2015] and isolated noradrenergic failure [Guaraldi et al 2011] result in the autonomic dysfunction seen in this disorder.

Pyramidal signs and symptoms usually develop after manifestations of autonomic dysfunction; however, gait difficulties have been reported as the first manifestations [Finnsson et al 2015]. Pyramidal manifestations include signs of upper motor neuron dysfunction, often more prominent in the lower extremities (e.g., spastic weakness,

hypertonia, clonus, brisk deep tendon reflexes, and bilateral Babinski signs). Spasticity can cause muscle pain and joint contractures. Over time, pyramidal dysfunction extends to the upper extremities.

Cerebellar signs that typically appear at the same time as the pyramidal signs include gait ataxia, dysdiadochokinesia, intention tremor, dysmetria, and nystagmus. Upper extremity postural tremor accompanied by neck tremor (resulting in head titubation) or jaw tremor (affecting speech and chewing) can also be seen [Schwankhaus et al 1988].

Cognitive function is usually preserved or mildly impaired early in the disease course; however, dementia and psychiatric manifestations can occur as late manifestations [Dos Santos et al 2012, Finnsson et al 2015].

Additional features

- Pseudobulbar palsy with dysarthria, dysphagia, and forced crying and laughing [Quattrocolo et al 1997] may appear in the eighth or eighth decade, which can affect feeding and lead to aspiration pneumonia and/or malnutrition.
- Many individuals have sensory deficits starting in the lower limbs associated with loss of position and vibration sensation attributed to extensive involvement of the spinal cord.
- Sensorineural hearing loss is seen in rare cases [Schwankhaus et al 1994].

Neurophysiologic studies are normal (electromyogram, visual evoked potentials, nerve conduction studies) or demonstrate nonspecific findings (brain stem auditory evoked potentials, somatosensory evoked potentials) or both (electroencephalograms).

Laboratory findings (CSF analysis, measurements of catecholamines, peripheral nerve biopsy) are either normal or do not yield findings specific to this disorder.

Prognosis. Affected individuals may survive for decades after onset of symptoms. Motor manifestations are usually slowly progressive without acute exacerbations; however, some affected individuals report reversible worsening of cognitive function and gait with fever [Finnsson et al 2015].

Genotype-Phenotype Correlations

Differences in clinical findings and MRI features have been noted between individuals with *LMNB1* duplications and those with deletions upstream of *LMNB1*. Those with the upstream deletions have been found to have earlier age of onset and a lack of early dysautonomia, with less brain stem and cerebellar involvement and spinal cord narrowing [Mezaki et al 2018, Nmezi et al 2019].

Penetrance

The disease presents in the fourth to fifth decade of adulthood, with equal frequency in males and females. Penetrance is not known but is thought to be 100%.

Nomenclature

LMNB1-related ADLD was originally referred to as "autosomal dominant leukodystrophy mimicking chronic progressive multiple sclerosis" or "adult-onset leukodystrophy simulating chronic progressive multiple sclerosis" [Eldridge et al 1984, Schwankhaus et al 1994]. In later publications, the disorder has been called "adult-onset autosomal dominant leukodystrophy with autonomic symptoms" [Melberg et al 2006] or referred to only as "autosomal dominant leukodystrophy" (ADLD) without any further definition.

Prevalence

The exact prevalence of *LMNB1*-related ADLD is unknown. Published reports include 33 families with more than 70 affected individuals; it is likely that many more unpublished families have now been identified.

Families of European, Middle Eastern, Asian, and Mexican ancestry have been reported.

Genetically Related (Allelic) Disorders

Heterozygous *de novo* missense variants in *LMNB1* have been reported in seven individuals with primary microcephaly, relative short stature, intellectual disability, and neurologic features [Cristofoli et al 2020]. (Note: Intragenic *LMNB1* sequence variants are not known to be associated with ADLD.)

Differential Diagnosis

The differential diagnosis of *LMNB1*-related autosomal dominant leukodystrophy (ADLD) includes other leukodystrophies with adult onset as well as acquired demyelinating disorders such as multiple sclerosis.

Acquired Demyelinating Disorders

Multiple sclerosis (MS) is an inflammatory disease that affects central nervous system white matter. The age of presentation and combination of motor, cerebellar, and autonomic manifestations make this disorder in some instances similar to *LMNB1*-related ADLD [Eldridge et al 1984]. Unlike the brain MRI in *LMNB1*-related ADLD, the brain MRI in MS is characterized by multifocal lesions mainly around the periventricular area, brain stem, cerebellum, and spinal cord [Noseworthy et al 2000]. CSF contains high IgG and oligoclonal bands [Poser et al 1983]. Available data suggest that multiple sclerosis is inherited as a complex multifactorial disorder that results from the interaction of genetic and environmental factors.

Vitamin B_{12} deficiency. While the first manifestation of vitamin B_{12} deficiency is typically megaloblastic anemia, on occasion the first manifestations can be the neurologic findings of subacute combined degeneration involving the spinal cord (myelopathy, loss of position and vibration sensation, bladder incontinence, and gait ataxia), peripheral nerves, and brain (neuropsychiatric disturbance). These neurologic findings can be confused with those of *LMNB1*-related ADLD. In vitamin B_{12} deficiency, MRI may reveal T_2-weighted hyperintensities in the spinal cord; these are mainly cervical and localized, not diffuse as in *LMNB1*-related ADLD.

Because untreated vitamin B_{12} deficiency is associated with progressive neurologic deterioration and because early detection and treatment can improve the long-term outcome, it is important that vitamin B_{12} deficiency be considered in the differential diagnosis of *LMNB1*-related ADLD [Rabhi et al 2011, Devalia et al 2014, Issac et al 2015].

Hereditary Disorders

Table 2. Genes and Disorders of Interest in the Differential Diagnosis of *LMNB1*-Related Autosomal Dominant Leukodystrophy (ADLD)

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder		
			Overlapping w/ *LMNB1*-related ADLD	Distinguishing from *LMNB1*-related ADLD	
				MRI Findings	Other Features
ABCD1	Adrenomyeloneuropathy (AMN) (See X-Linked Adrenoleukodystrophy.)	XL	Slowly progressing paraparesis, sphincter control abnormalities, & sexual dysfunction in males & some heterozygous females	~20% of those w/AMN develop rapidly progressive brain involvement. ~85% have symmetric ↑ T_2-weighted signal usually in parieto-occipital region w/contrast enhancement at the advancing margin.	Impaired adrenocortical function in 2/3s of affected persons
ATXN2 *ATXN3*	SCA2 & SCA3 [1]	AD	Cerebellar gait ataxia, autonomic disturbances, pyramidal involvement, & dysarthria	No specific radiologic changes	Nystagmus, peripheral neuropathy, abnormal movements, & seizures
CSF1R	*CSF1R*-related adult-onset leukoencephalopathy w/axonal spheroids & pigmented glia	AD	Impaired balance, spasticity, gait apraxia, ataxia, & urinary incontinence.	Bifrontal or bifrontoparietal T_2-weighted hyperintensities often involving periventricular areas. (Unlike *LMNB1*-related ADLD, periventricular rims are not less affected.) Thin corpus callosum w/T_2-weighted hyperintense lesions; cerebral atrophy manifesting as enlarged ventricles	Frontal lobe syndrome & personality changes (which are not typical in ADLD) are predominant & usually appear early. CT shows calcifications.
DARS2	Leukoencephalopathy w/brain stem & spinal cord involvement & lactate elevation	AR	Progressive spasticity, cerebellar ataxia, dorsal column abnormalities. Dysarthria develops over time.	Lesions w/high T_2-weighted signal intensity in brain stem & spinal cord (usually in the dorsal columns & lateral corticospinal tracts) are typical, but cerebral WM can also be affected.	Personality changes, cognitive impairments, & memory decline
EIF2B1 *EIF2B2* *EIF2B3* *EIF2B4* *EIF2B5*	Adult onset type of childhood ataxia w/ central nervous system hypomyelination/ vanishing white matter	AR	Ataxia, spasticity w/↑ tendon reflexes; rapid deterioration during febrile illnesses	Bilateral confluent cerebral T_2-weighted hyperintensities. Part of the abnormal WM has a signal intensity close to that in CSF w/all sequences. Severe cerebral atrophy can be observed in adult-onset forms w/slow progression.	Cognitive decline & personality changes dominate. Often ovarian failure. Optic atrophy & epilepsy may occur.

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder		
			Overlapping w/ *LMNB1*-related ADLD	Distinguishing from *LMNB1*-related ADLD	
				MRI Findings	Other Features
GALC	Adult-onset Krabbe disease	AR	Affected persons present w/signs of pyramidal tract dysfunction; spastic paraparesis is a prominent sign. Peripheral neuropathy, dysarthria, & cerebellar ataxia are not unusual. [2]	Upper corticospinal tracts are always affected on T_2-weighted images – similar to abnormalities in asymptomatic persons w/*LMNB1*-related ADLD. However, in adult-onset Krabbe disease, these tracts are less often affected in the brain stem, esp in the medulla oblongata. ↑ T_2-weighted signal intensity is also seen periventricularly along trigonal wall & optic radiations & in posterior corpus callosum. [3] Thus, the abnormalities have a more posterior distribution than in *LMNB1*-related ADLD.	
GBE1	*GBE1* adult polyglucosan body disease	AR	Neurogenic bladder, spasticity & weakness from mixed upper & lower motor neuron involvement, sensory loss mainly in distal lower extremities	Paraventricular, subcortical, & deep slowly progressive WM changes that may incl involvement of the upper pons, superior cerebellar peduncles, dentate nuclei, & anterior medulla (incl the olives) often extending to the level of the cervico-medullary junction; slowly progressive cerebral, cerebellar, & spinal cord atrophy	
GFAP	Adult form of Alexander disease	AD	Pyramidal signs (spasticity, hyperreflexia, positive Babinski sign), cerebellar ataxia, dysautonomia	Focal T_2-weighted hyperintensities in the brain stem, cerebellar WM, & cervical spinal cord w/mass effect & contrast enhancement in active phases. After the active phase, atrophy develops. Supratentorial WM abnormalities may occur.	Bulbar & pseudobulbar signs are early or only signs in adult-onset Alexander disease but very late signs in *LMNB1*-related ADLD.

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; MOI = mode of inheritance; SCA = spinocerebellar ataxia; WM = while matter; XL = X-linked

1. See also Hereditary Ataxia Overview.

2. Debs et al [2013]

3. Cousyn et al [2019]

Management

No clinical practice guidelines for *LMNB1*-related autosomal dominant leukodystrophy (ADLD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *LMNB1*-related ADLD, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *LMNB1*-related Autosomal Dominant Leukodystrophy (ADLD)

System/Concern	Evaluation	Comment
Neurologic	Neurologist	For evidence of autonomic dysfunction (e.g., orthostatic hypotension), abnormal tone, &/or tremor
Urogenital dysfunction	Urologic eval	For urinary dysfunction, recurrent urinary tract infection, & erectile dysfunction
Bowel dysfunction	Gastroenterology assessment	
Upper motor neuron dysfunction	Assessment by rehab specialists	To incl equipment needs
Cognitive function	Neuropsychological assessment	
Jaw tremor & pseudobulbar palsy	Eval of chewing, speech, & swallowing	
Hearing loss	Audiologic assessment	
Genetic counseling	By genetics professionals [1]	To inform patients & their families re nature, MOI, & implications of ADLD in order to facilitate medical & personal decision making
Family support & resources	Assess need for: • Social work involvement for family support; • Home nursing referral.	

MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *LMNB1*-related Autosomal Dominant Leukodystrophy (ADLD)

Manifestation/ Concern	Treatment	Considerations/Other
Neurogenic bladder	• Address recurrent urinary tract infections w/attn to bladder regimens for managing neurogenic bladders, which may (rarely) require antibiotic prophylaxis. • Spasmolytics (e.g., solifenacine succinate) for urinary urgency	
Constipation	Good hydration & dietary fiber	Stool softeners (e.g., docusate) or a laxative may be needed.
Orthostatic hypotension	• Pharmacologic treatment (mineralocorticoids such as fludrocortisone or vasopressors such as hydrochloride) • Compression stockings • PT (to help w/rising from supine positions) • ↑ salt in the diet	
Erectile dysfunction	Medical treatment w/sildenafil	
Anhidrosis	Avoid overheating.	• Can use cooling vests, fans, air conditioning • Intensive mgmt of infections should incl adequate antipyretic treatment.

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	• Medications to help ↓ muscle tone such as oral baclofen or diazepam (GABA agonists) or injectable botulinum toxin for focal muscle spasticity • Individualized PT regimen to improve joint mobility & function	
Ataxia	• Strategies to minimize falls & ↑ strength • Adaptive equipment such as walkers or wheelchairs	
Feeding difficulties assoc w/ pseudobulbar palsy	Speech therapy & appropriate feeding interventions to assure adequate nutrition while preventing aspiration pneumonia	
Cognitive dysfunction	• Work w/social worker & financial planner to help anticipate issues of guardianship that may accompany progressive decline. • Family & patient support/advocacy groups to help address progressive psychosocial consequences of ADLD	

PT = physical therapy

Surveillance

Recommended surveillance:

- Routine assessment of weight, nutrition, and feeding; pulmonary status (re possible recurrent pneumonia); bladder and erectile function; psychosocial well-being; and medications and dosage to avoid iatrogenic polypharmacy
- At least annual assessment by multidisciplinary specialists including a neurologist for disease manifestations and progression; and by a physiatrist, orthopedist, physical therapist, and occupational therapist to address orthopedic, equipment, and functional needs

Agents/Circumstances to Avoid

Because disease manifestations may be exacerbated with fever and infection, care should be taken to avoid whenever possible exposure to those with infections.

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

LMNB1-related autosomal dominant leukodystrophy (ADLD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, all individuals diagnosed with *LMNB1*-related ADLD whose parents have undergone molecular genetic testing have the disorder as the result of an *LMNB1* duplication (or a deletion upstream of *LMNB1)* inherited from an affected parent.
- To date, a *de novo LMNB1* duplication (or deletion upstream of *LMNB1*) has not been reported in a proband; however, it should be noted that not all affected individuals have parents available for testing.
- If the proband appears to be the only affected family member (i.e., a simplex case) and the proband's parents are available for testing, molecular genetic testing is recommended for the parents to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *LMNB1*-related ADLD may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or has an *LMNB1* duplication (or deletion upstream of *LMNB1*) , the risk to the sibs of inheriting the pathogenic variant is 50%; clinical severity may vary within families.
- If the *LMNB1* duplication (or deletion upstream of *LMNB1*) identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but have not been tested for the pathogenic variant identified in the proband, sibs of the proband are still presumed to be at increased risk for *LMNB1*-related ADLD because of the possibility of age-related penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *LMNB1*-related ADLD has a 50% chance of inheriting the *LMNB1* duplication (or deletion upstream of *LMNB1*).

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has an *LMNB1* duplication (or deletion upstream of *LMNB1*), his or her family members may be at risk.

Related Genetic Counseling Issues

MRI findings suggestive of leukodystrophy may be seen many years before clinical manifestation of disease. This should perhaps be communicated to relatives at risk, as many persons may undergo MRI of the brain and spinal cord for a variety of unrelated reasons.

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the *LMNB1* duplication (or deletion upstream of *LMNB1*) has been identified in an affected family member.
- Potential consequences of such testing (including but not limited to socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of *LMNB1*-related ADLD, it is appropriate to consider testing of symptomatic individuals regardless of age.

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the causative pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *LMNB1*-related ADLD 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. For more information, see the National Society of Genetic Counselors position statement on prenatal testing for adult-onset conditions.

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.

- **ADLD Center**
  2609 Crooks Road
  Suite 116
  Troy 48084
  www.adld.center/

- **European Leukodystrophy Association (ELA)**
  ela-asso.com
- **Leukodystrophy Australia**
  Australia
  Phone: 1800 141 400
  Email: info@leuko.org.au
  leuko.org.au
- **United Leukodystrophy Foundation**
  Phone: 815-748-0844
  Email: office@ulf.org
  ulf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
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  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. LMNB1-Related Autosomal Dominant Leukodystrophy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LMNB1	5q23.2	Lamin-B1	Human Intermediate Filament Database LMNB1 LMNB1 database	LMNB1	LMNB1

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 LMNB1-Related Autosomal Dominant Leukodystrophy (View All in OMIM)

150340	LAMIN B1; LMNB1
169500	LEUKODYSTROPHY, DEMYELINATING, ADULT-ONSET, AUTOSOMAL DOMINANT, TYPICAL; ADLDTY

Molecular Pathogenesis

*LMNB*1 encodes lamin-B1, a member of the intermediate filament family of structural proteins and an integral component of the nuclear lamina. It not only provides structural integrity to the nucleus but also plays a role in essential cellular processes such as transcription, DNA replication, DNA repair, and epigenetic regulation [Butin-Israeli et al 2012, Stancheva & Schirmer 2014]. Lamin-B1 is widely expressed in various cell types and shows high levels of expression in the brain [Jung et al 2013].

Both duplications of *LMNB1* and deletions affecting the promoter upstream of *LMNB1* are thought to result in increased levels of lamin-B1 and, as such, there is no abnormal gene product, just an overexpression of the wild type protein. In individuals with *LMNB1*-related adult-onset autosomal dominant leukodystrophy (ADLD):

- Fibroblasts have exhibited nuclear abnormalities, increased nuclear stiffness, and alterations in RNA splicing [Ferrera et al 2014, Bartoletti-Stella et al 2015].
- Overexpression in muscle cells had an effect on actin and sarcomere function [Columbaro et al 2013].
- Overexpression of lamin-B1 reduces the ability of astrocytes to support oligodendrocytes during the myelination process [Ratti et al 2021].

Overexpression of lamin-B1 was found to have deleterious effects in model organisms.

- **Fruit fly model.** Overexpression of lamin-B1 resulted in lethality and a degenerative phenotype [Padiath et al 2006].
- **ADLD mouse model.** Targeted overexpression of lamin-B1 in oligodendrocytes, but not in neurons or astrocytes, resulted in demyelination and an age-dependent motor dysfunction reminiscent of the human disease [Heng et al 2013].
- **Mouse model.** Overexpression of lamin-B1 caused age-dependent motor dysfunction, but not autonomic cardiovascular dysfunction, indicating that oligodendrocyte dysfunction alone may not be the underlying cause for the entire phenotypic spectrum of ADLD [Lo Martire et al 2018].
- **Independently derived oligodendrocyte-specific lamin-B1 overexpressing mouse model.** Vacuolar demyelination of the spinal cord linked to an age-dependent reduction in lipid synthesis was responsible for the degenerative phenotype [Rolyan et al 2015].

Mechanism of disease causation. The pathology in *LMNB1*-related ADLD is thought to be due to gain of abnormal function associated with increased levels of lamin-B1.

Chapter Notes

Author Notes

Raili Raininko
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Dr Raininko has ceased participation in clinical neuroradiologic work but continues in research projects. One of the main research areas is inherited neurologic diseases in children and adults. Disease development and mechanism have been investigated in collaboration with clinicians, geneticists, and pathologists.

Michael Gosky
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Mr Gosky recently completed his Masters degree in genetic counseling at the University of Pittsburgh and is currently a genetic counselor at the University of Kentucky. His research interests include neuroscience and genetics.

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The major focus of the Padiath lab is to understand the molecular mechanisms underlying various neurologic diseases with an emphasis on the disorders of myelin known as leukodystrophies. This work involves the use of clinical-based family studies to identify disease-related genes and the development of animal and cell culture models to elucidate disease mechanisms. Dr Padiath identified lamin B1 duplications as the cause of ADLD;

understanding the molecular mechanisms of this disease remains an important area of research in his lab at the University of Pittsburgh.

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