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ALS2-Related Disorders

Richard W Orrell, BSc, MD, FRCP
University Department of Clinical Neurosciences
Institute of Neurology
University College London
London, United Kingdom
r.orrell@ucl.ac.uk

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Summary

Clinical characteristics. *ALS2*-related disorders involve retrograde degeneration of the upper motor neurons of the pyramidal tracts and comprise a clinical continuum from infantile ascending hereditary spastic paraplegia (IAHSP), to juvenile forms without lower motor neuron involvement (juvenile primary lateral sclerosis [JPLS]), to forms with lower motor neuron involvement (autosomal recessive juvenile amyotrophic lateral sclerosis [JALS]).

- IAHSP is characterized by onset of spasticity with increased reflexes and sustained clonus of the lower limbs within the first two years of life, progressive weakness and spasticity of the upper limbs by age seven to eight years, and wheelchair dependence in the second decade with progression toward severe spastic tetraparesis and a pseudobulbar syndrome.
- JPLS is characterized by onset and loss of ability to walk during the second year of life, progressive signs of upper motor neuron disease, wheelchair dependence by adolescence, and later loss of motor speech production.
- JALS is characterized by onset during childhood (mean age of onset 6.5 years), spasticity of facial muscles, uncontrolled laughter, spastic dysarthria, spastic gait, moderate muscle atrophy (variably present), bladder dysfunction, and sensory disturbances; some individuals are bedridden by age 12 to 50 years.

Diagnosis/testing. Results of electrophysiology studies in *ALS2*-related disorders vary by phenotype; MRI shows brain changes in older individuals with IAHSP. Pathogenic variants in *ALS2* have been found in four of 11 families with IAHSP; no other genes/loci are known to be associated with these disorders.

Management. *Treatment of manifestations:* Physical and occupational therapy to promote mobility and independence and use of computer technologies and devices to facilitate writing and voice communication.

Prevention of secondary complications: Early detection and treatment of hip dislocation and/or spine deformities prevent further complications.

Surveillance: Evaluation for feeding difficulties and modification of diet to reduce risk of aspiration.

Genetic counseling. *ALS2*-related disorders are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk are possible if both pathogenic variants have been identified in an affected family member.

GeneReview Scope

***ALS2*-Related Disorders: Included Phenotypes** [1]

- Infantile-onset ascending hereditary spastic paralysis
- Juvenile primary lateral sclerosis
- Autosomal recessive juvenile amyotrophic lateral sclerosis

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

Diagnosis

ALS2-related disorders involve retrograde degeneration of the upper motor neurons of the pyramidal tracts and comprise a clinical continuum that includes:

- Infantile ascending hereditary spastic paraplegia (IAHSP),*
- Juvenile forms without lower motor neuron involvement (juvenile primary lateral sclerosis, or JPLS),* and
- Forms with lower motor neuron involvement (autosomal recessive juvenile amyotrophic lateral sclerosis, or JALS).

The different phenotypes reported in the literature are summarized.

*Note: In some instances, the same entity may be called either juvenile primary lateral sclerosis or IAHSP.

Suggestive Findings

An *ALS2*-related disorder **should be suspected** in individuals with the following phenotypes, electrophysiologic findings, and neuroimaging findings:

Phenotypes

Infantile-onset ascending hereditary spastic paralysis (IAHSP) is characterized by the following features [Lesca et al 2003]:

- Onset of spasticity with increased reflexes and sustained clonus of the lower limbs within the first two years of life
- Progressive weakness and spasticity of the upper limbs by age seven to eight years
- Wheelchair dependence in the second decade, with progression toward severe spastic tetraparesis and a pseudobulbar syndrome
- Preservation of cognitive function

Juvenile primary lateral sclerosis (JPLS) is characterized by the following features [Gascon et al 1995, Yang et al 2001]:

- Onset during the second year of life
- Loss of ability to walk in the second year of life
- Slowly progressive uncomplicated signs of upper motor neuron disease
- Wheelchair dependence by adolescence
- Later loss of motor speech production
- Preservation of cognitive function

Autosomal recessive juvenile amyotrophic lateral sclerosis (JALS) (also known as ALS2) is characterized by the following features [Ben Hamida et al 1990]:

- Onset during childhood (mean age of onset 6.5 years; range 3-20 years)
- Spasticity of facial muscles with uncontrolled laughter and spastic dysarthria; spastic gait; in some individuals, mild atrophy of the legs and hands
- Variably present moderate muscle atrophy, absence of fasciculations, bladder dysfunction, and sensory disturbances
- Some individuals bedridden by age 12 to 50 years (no information is available on age of wheelchair dependence)
- Preservation of cognitive function not confirmed

Electrophysiologic Findings

Table 1 shows the results of various electrophysiologic studies in the different phenotypes of *ALS2*-related disorders.

Table 1.

Electrophysiologic Studies in *ALS2*-Related Disorders by Phenotype

Study	Phenotype		
	IAHSP	**JPLS**	**JALS**
MEP [1]	Severe dysfunction of the corticospinal tracts [2]	NA [3]	Absent or reduced action potential, suggesting dysfunction of corticospinal tracts [4]
SSEP [5]	Normal in early stages; abnormal in later stages	Poorly configured; normal central conduction	NA [3]
EMG [6]	No signs of denervation	No signs of denervation	Signs of denervation
NCV [7]	Normal	Normal	Normal
VEP [8]		Normal	
BAER [9]		Normal	
TCMS [10]		No motor evoked potentials	

1. Motor evoked potentials
2. Primitive, pure degeneration of the upper motor neurons
3. Not available
4. Kress et al [2005]
5. Somatosensory evoked potentials
6. Electromyography
7. Nerve conduction velocities
8. Visual evoked potentials
9. Brain stem auditory evoked potentials
10. Transcranial magnetic stimulation

Neuroimaging Findings

IAHSP. Magnetic resonance imaging (MRI) is normal in children.

Older individuals have:

- Brain cortical atrophy predominant in the motor areas
- T_2-weighted bilateral punctate hyperintense signals in the corticospinal pathways of the posterior arms of the internal capsule and brain stem.

In addition, it is common to find T_2- or FLAIR-weighted hyperintensities of periventricular areas and aspects of spinal cervical atrophy that are often seen in other hereditary spastic paraplegias (HSPs).

JPLS. CT and MRI scans of brain and spinal cord are normal.

JALS. MRI studies of brain and spinal cord are normal [Kress et al 2005, Shirakawa et al 2009].

Establishing the Diagnosis

The diagnosis of an *ALS2*-related disorder **is established** in a proband with the identification of biallelic pathogenic variants in *ALS2* on molecular genetic testing (see Table 1).

Molecular testing approaches can include **single-gene testing** and use of a **multi-gene panel.**

- **Single-gene testing.** Sequence analysis of *ALS2* is performed first followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found. Note that while no *ALS2* exon or whole-gene deletions/duplications have been reported to date, loss of *ALS2* function due to these mechanisms would be expected to cause disease; thus, use of gene-targeted deletion/duplication analysis in this instance is a reasonable option.
- **A multi-gene panel** that includes *ALS2* 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 over time. (2) Some multi-gene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multi-gene panel provides the best opportunity to identify the causative gene at the most reasonable cost.

Table 2.

Molecular Genetic Testing Used in *ALS2*-Related Disorders

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by This Method
ALS2	Sequence analysis [3]	All sequence variants reported to date
	Gene-targeted deletion/duplication analysis [4]	None reported [5]

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. 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 that may be used can 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.
5. No data on detection rate of gene-targeted deletion/duplication analysis are available; however, loss of *ALS2*

function due to a large deletion or duplication is expected to cause disease.

Clinical Characteristics

Clinical Description

Pathogenic variants in *ALS2* are responsible for a retrograde degeneration of the upper motor neurons of the pyramidal tracts, leading to a clinical continuum from infantile ascending hereditary spastic paraplegia to juvenile forms without lower motor neuron involvement (juvenile primary lateral sclerosis) or with lower motor neuron involvement (autosomal recessive juvenile amyotrophic lateral sclerosis).

Infantile ascending hereditary spastic paraplegia (IAHSP). Spastic paraplegia begins during the first two years of life and extends to upper limbs within the next few years. Manifestations of the disease may start as early as the first year of life. During the first decade of life, the disease progresses to tetraplegia, anarthria, dysphagia, and slow eye movements.

Feeding difficulties, especially in swallowing liquids, may manifest in the second decade; however, those few individuals with long-term follow up who have reached their 30s have neither experienced recurrent bronchopneumonia nor required feeding gastrostomy. Some individuals are reported to require feeding by gastrostomy tube and to lose bladder and sphincter functions in the advanced state [Verschuuren-Bemelmans et al 2008].

Overall, IAHSP is compatible with long survival. Cognitive function is preserved.

Juvenile primary lateral sclerosis (JPLS). Examination reveals upper motor neuron findings of pseudobulbar palsy and spastic quadriplegia without dementia or cerebellar, extrapyramidal, or sensory signs. In addition, affected individuals exhibit a diffuse conjugate saccadic gaze paresis, especially severe on downgaze. Some of these children are never able to walk independently, while others are delayed in walking and then lose the ability to walk independently by the first decade of life. Speech deterioration starts between ages two and ten years. No cognitive deterioration is reported. Survival is variable.

Intrafamilial variability can be considerable: in one family with two affected sibs with onset in early childhood, one began using a wheelchair at age two years (and was alive at age 42 years); the other began using a wheelchair at age 50 years (and was alive at age 55 years) [Mintchev et al 2009].

Autosomal recessive juvenile amyotrophic lateral sclerosis (JALS or ALS2) [Ben Hamida et al 1990, Hentati et al 1994]. Onset is between ages three and 20 years. All affected show a spastic pseudobulbar syndrome together with spastic paraplegia. Peroneal muscular atrophy is observed in some, but not all, individuals. Atrophy or fasciculation of the tongue does not occur. At the time of the description of clinical symptoms, three individuals from one family were bedridden by age 12, 20, and 50 years, but another remained ambulatory until age 50 years.

Other. Two families with homozygous *ALS2* pathogenic variants have been reported to demonstrate generalized dystonia and cerebellar signs [Sheerin et al 2014].

Genotype-Phenotype Correlations

Both IAHSP and JPLS have been associated with truncating *ALS2* variants. Generally, the IAHSP and JPLS phenotypes are uniform within families (based on data regarding individuals from 9 families).

Nomenclature

See Amyotrophic Lateral Sclerosis Overview.

Prevalence

No data on prevalence are available, but *ALS2*-related disorders are probably currently underdiagnosed.

ALS2-related disorders have been described in individuals from a variety of ethnic backgrounds.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *ALS2*.

Differential Diagnosis

Hereditary Spastic Paraplegia (HSP)

For a detailed discussion of HSP and the differential diagnosis of HSP, see the Hereditary Spastic Paraplegia Overview.

The hereditary spastic paraplegias are clinically and genetically heterogeneous disorders characterized by insidiously progressive lower extremity weakness and spasticity. Hereditary spastic paraplegia may be transmitted in an autosomal dominant, autosomal recessive, X-linked, or maternally inherited (mitochondrial) manner.

Children with autosomal dominant HSP and with congenital onset of spasticity (SPG4, caused by pathogenic variants in *SPAST* encoding spastin and SPG3A, caused by pathogenic variants in *ATL1* encoding atlastin) have a non-progressive or very slowly progressive course, whereas in the most common presentation of HSP with onset of spasticity and weakness in adulthood, the course is clearly progressive.

IAHSP without *ALS2* pathogenic variants. Genetic heterogeneity has been demonstrated by Lesca et al [2003] by the fact of only four of 11 families with IAHSP have *ALS2* pathogenic variants. No other genes/loci causing this phenotype have been identified.

ARHSP. In general, in autosomal recessive hereditary spastic paraplegia (ARHSP) with onset during childhood, the progression is less severe and spasticity predominates over weakness. Pseudobulbar involvement in *ALS2*-related disorders clearly delineates it from all the other genetic forms of spastic paraparesis. In contrast, in ARHSP, muscle weakness predominates over spasticity, onset is clearly apparent during the first decade, and involvement of upper limbs and bulbar function is invariable. The role of *ALS2* pathogenic variants in ARHSP has not yet been investigated.

Normal brain white matter on MRI rules out the diagnosis of leukodystrophy (see Leukodystrophy Overview).

Metabolic investigations rule out other metabolic causes of progressive ARHSP (very long chain fatty acids [see X-Linked Adrenoleukodystrophy], arylsulfatase A deficiency, mitochondrial dysfunction [see Mitochondrial Disorders Overview]); however, decline in behavior or cognitive function is frequently observed in these conditions.

Primary lateral sclerosis (PLS) is defined as the presence of slowly progressive, uncomplicated signs of upper motor neuron disease in persons in whom all other known causes of spasticity have been eliminated. PLS has been described in adults with an isolated degenerative process of the upper motor neurons, with sporadic occurrence [Pringle et al 1992]. No *ALS2* pathogenic variants were identified in a study of 51 Dutch persons with adult-onset PLS [Brugman et al 2007].

Al-Saif et al [2012] described a consanguineous family from Saudi Arabia having four sibs with infantile-onset PLS with severe progression requiring wheelchair by age 12 and associated with a homozygous splice junction pathogenic variant (c.499-1G>T) in *ERLIN2* [OMIM 611225].

Amyotrophic Lateral Sclerosis (ALS)

For a detailed discussion of ALS and the differential diagnosis of ALS, see Amyotrophic Lateral Sclerosis Overview.

ALS is a progressive neurodegenerative disease involving both the upper motor neurons (UMN) and lower motor neurons (LMN). LMN signs include weakness, muscle wasting, muscle cramps, fasciculations, and eventually hyporeflexia. UMN signs include hyperreflexia, extensor plantar response, increased muscle tone, and weakness in a topographic representation. Approximately 25 genes are currently thought to be associated with ALS; of these, *ALS2*, *SETX* (ALS4), and *SIGMAR1* (ALS16) are associated with juvenile onset [Marangi & Traynor 2015].

ALS4 is an autosomal dominant form of ALS, with signs and symptoms of both upper and lower motor neuron involvement and onset before age 25 years. This has also been described as a distal hereditary motor neuropathy with pyramidal signs. Individuals with ALS4 usually have onset before age 25 years, a slow rate of progression, and a normal life span [Chen et al 2004]. ALS4 is caused by mutation of *SETX*.

ALS5 (also known as type 1 autosomal recessive ALS) very closely resembles typical ALS of any age of onset and is the most prevalent form of autosomal recessive ALS, having been identified in several ethnic groups (North African, South Asian, and European). This form of recessive ALS was mapped to 15q by Hentati et al [1998].

ALS16. Al-Saif et al [2011] reported a consanguineous family from Saudi Arabia with juvenile ALS (onset age 1-2 years, slowly progressing to use of a wheelchair by age 20 years) with a homozygous pathogenic missense variant (c.304G>C, p.Glu102Gln) in *SIGMAR1* [OMIM 614373].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *ALS2*-related disorder, the following evaluations are recommended:

- Family history
- Neurologic examination, including assessment of eye movements, speech, fine motor and gross motor function, swallowing
- Detailed dietary and feeding assessment as needed
- Orthopedic and rehabilitation assessment as needed
- Consultation with a medical geneticist and/or genetic counselor

Treatment of Manifestations

The following are appropriate:

- Physical and occupational therapy to promote mobility and independence
- Aids for mobility and limb function
- Use of computer technologies and devices adapted to facilitate writing and voice communication

Surveillance

Routine monitoring:

- For feeding difficulties and assessment of diet to assure that the risk of aspiration is reduced
- For early detection and treatment of hip dislocation and/or spine deformities

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 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, 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

ALS2-related disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *ALS2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with *ALS2*-related disorders have marked motor disability and have not been known to reproduce.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ALS2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ALS2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier 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 carriers or at risk of being carriers.

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 *ALS2* pathogenic variants have been identified in an affected family member, prenatal testing or preimplantation genetic diagnosis for a pregnancy at increased risk for an *ALS2*-related disorder may be an option that a couple may wish to consider.

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.

- **National Library of Medicine Genetics Home Reference**
  Infantile-onset ascending hereditary spastic paralysis
- **National Library of Medicine Genetics Home Reference**
  Juvenile primary lateral sclerosis
- **Amyotrophic Lateral Sclerosis Association (ALS Association)**
  27001 Agoura Road
  Suite 250
  Calabasas Hills CA 91301-5104
  Phone: 800-782-4747 (Toll-free Patient Services); 818-880-9007
  Fax: 818-880-9006
  Email: alsinfo@alsa-national.org
  www.alsa.org
- **Amyotrophic Lateral Sclerosis Society of Canada**
  3000 Steeles Avenue East
  Suite 200
  Markham Ontario L3R 4T9
  Canada
  Phone: 800-267-4257 (toll-free); 905-248-2052
  Fax: 905-248-2019
  www.als.ca
- **Motor Neurone Disease Association**
  PO Box 246
  Northampton NN1 2PR
  United Kingdom
  Phone: 01604250505
  Fax: 01604 624726/638289
  Email: enquiries@mndassociation.org
  www.mndassociation.org
- **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)
  Hereditary Spastic Paraplegia Information Page
- **National Library of Medicine Genetics Home Reference**
  Amyotrophic lateral sclerosis

- **Spastic Paraplegia Foundation, Inc.**
  7700 Leesburg Pike
  Ste 123
  Falls Church VA 22043
  Phone: 877-773-4483 (toll-free)
  Email: information@sp-foundation.org
  sp-foundation.org

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.

ALS2-Related Disorders: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus Specific	HGMD
ALS2	*ALS2*	2q33.1	Alsin	alsod/ALS2 genetic mutations ALS mutation database (ALS2) ALS2 database	ALS2

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B.

OMIM Entries for ALS2-Related Disorders (View All in OMIM)

205100	AMYOTROPHIC LATERAL SCLEROSIS 2, JUVENILE; ALS2
606352	ALSIN
606353	PRIMARY LATERAL SCLEROSIS, JUVENILE; PLSJ
607225	SPASTIC PARALYSIS, INFANTILE-ONSET ASCENDING; IAHSP

Gene structure. The longer transcript variant of *ALS2* (NM_020919.3) comprises 34 exons in a genomic region of 83 kb. Alternative splicing gives rise to a 184-kd full-length form of 1,657 amino acids and a smaller, alternatively spliced transcript of 396 amino acids (NM_001135745.1, NP_001129217.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Nearly 50 pathogenic variants, many homozygous, have been reported in individuals with *ALS2*-related disorders. These variants include frameshift, nonsense, splice site, and missense variants. See Table 3 (pdf) and Figure 1.

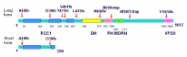

Figure 1.

Schematic representation of the Alsin protein domain structure with reported amino acid changes indicated Alsin protein with RCC1 (regulator of chromatin condensation)-like domain (RLD), DH/PH (Dbl and pleckstrin homology), and VPS9 (vacuolar protein (more...)

Normal gene product. Sequence comparisons suggest that *ALS2* encodes the protein alsin which contains three guanine nucleotide exchange factor (GEF) domains: RCC1(regulator of chromatin condensation)-like domain (RLD); the Dbl homology and pleckstrin homology (DH/PH); and the

vacuolar protein sorting 9 (VPS9) (see Figure 1). GEF activates one or more small GTPases, facilitating the releasing of GDP and exchange for GTP. Alsin acts as a GEF for Rab5, a GTPase implicated in endosomal trafficking [Otomo et al 2003, Hadano et al 2007]. Alsin acts on Rac1, a G protein involved in actin cytoskeleton remodeling [Topp et al 2004, Kanekura et al 2005], and recruits active Rac1 to membrane ruffles facilitating Rac1-activated endocytosis [Kunita et al 2007].

Endogenous alsin is enriched in nerve tissue where it is peripherally bound to the cytoplasmic face of endosomal membranes [Otomo et al 2003, Yamanaka et al 2003, Kunita et al 2004, Topp et al 2004]. Alsin is also present in membrane ruffles and lamellipodia [Topp et al 2004], suggesting that alsin is involved in membrane transport events, potentially linking endocytic processes and actin cytoskeleton remodeling.

The function of alsin in the nervous system has been tested in alsin-deficient mice and the primary neurons from them. Neuropathologic analysis exhibited mild axonal degeneration in the dorsolateral [Yamanaka et al 2006] or distal corticospinal tracts [Deng et al 2007, Gros-Louis et al 2008], or progressive loss of cerebellar Purkinje cells with decreased number of motor axons from lumbar spinal cord [Hadano et al 2006]. Modest behavioral abnormalities observed in alsin-deficient mice included motor slowness and/or decreased motor coordination measured by rotarod performance [Cai et al 2005, Deng et al 2007, Yamanaka et al 2006]. Alsin-deficient mice have normal life span and a far milder phenotype than that observed in humans with *ALS2* pathogenic variants.

Abnormal gene product. Mutated alsin and a naturally truncated alsin isoform are rapidly degraded when expressed in cultured human cells, including lymphocytes and fibroblasts derived from individuals with *ALS2* pathogenic variants. Thus, pathogenic variants in *ALS2* linked to early-onset motor neuron disease uniformly produce loss of activity through decreased protein stability of this endosomal GEF [Yamanaka et al 2003].

Some reported *ALS2* pathogenic variants causing motor neuron diseases are reported to be associated with a loss of protein stability [Yamanaka et al 2003], which leads to reduction or loss of all three potential GEF domains. A current research focus is the role of alsin as a Rab5-GEF and its involvement in endosomal dynamics. It is premature to discount roles for the other GEF domains as well as corresponding GTPases in understanding the role of alsin in the death of upper motor neurons beginning in early postnatal life.

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Chapter Notes

Author History

Enrico S Bertini, MD; Ospedale Bambino Gesu, Rome (2005-2016)
Odile Boespflug-Tanguy, MD, PhD; Institut National de la Santé et de la Recherche Médicale, Clermont-Ferrand (2005-2016)
Don W Cleveland, PhD, University of California San Diego (2005-2016)
Eleonore Eymard-Pierre, PhD; Institut National de la Santé et de la Recherche Médicale, Clermont-Ferrand (2005-2016)
Richard W Orrell, BSc, MD, FRCP (2016-present)
Koji Yamanaka, MD, PhD; RIKEN Brain Science Institute, Wako (2005-2016)

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