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ALS2-Related Disorder

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Summary

Clinical characteristics

ALS2-related disorder involves retrograde degeneration of the upper motor neurons of the pyramidal tracts and comprises a clinical continuum of the following three phenotypes:

- **Infantile ascending hereditary spastic paraplegia (IAHSP),** 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 caused by progressive cranial nerve involvement
- **Juvenile primary lateral sclerosis (JPLS),** characterized by upper motor neuron findings of pseudobulbar palsy and spastic quadriplegia without dementia or cerebellar, extrapyramidal, or sensory signs
- **Juvenile amyotrophic lateral sclerosis (JALS or ALS2),** characterized by onset between ages three and 20 years. All affected individuals show a spastic pseudobulbar syndrome (spasticity of speech and swallowing) together with spastic paraplegia. Some individuals are bedridden by age 12 to 50 years.

Diagnosis/testing

The diagnosis of *ALS2*-related disorder is established in a proband with suggestive findings and biallelic pathogenic variants in *ALS2* identified on molecular genetic testing.

Management

Treatment of manifestations: Management by multidisciplinary specialists including neurology, orthopedics, physical therapy, occupational therapy, speech and language therapy, and feeding specialists (gastroenterology, nutrition) is recommended. Physical and occupational therapy promote mobility and independence; use of computer technologies and devices can facilitate writing and voice communication. Early detection and treatment of hip dislocation and/or spine deformities can prevent further complications.

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Surveillance: Routine reevaluation by the multidisciplinary care providers to monitor progression of existing findings and development of new findings.

Genetic counseling

ALS2-related disorder is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ALS2* pathogenic variant, each sib of an affected individual has at conception 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. Once both *ALS2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

ALS2-Related Disorder: Included Phenotypes [1]
• Infantile-onset ascending hereditary spastic paralysis (IAHSP) • Juvenile primary lateral sclerosis (JPLS) • Juvenile amyotrophic lateral sclerosis (JALS)

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

Diagnosis

No consensus clinical diagnostic criteria for *ALS2*-related disorder have been published.

ALS2-related disorder comprises a phenotypic continuum of three phenotypes previously thought to be distinct entities: infantile-onset ascending hereditary spastic paralysis (IAHSP), juvenile primary lateral sclerosis (JPLS), and juvenile amyotrophic lateral sclerosis (JALS).

Suggestive Findings

ALS2-related disorder **should be suspected** in individuals with the following clinical, electrophysiologic, and neuroimaging findings and family history.

Clinical Findings

- Childhood onset of progressive upper motor neuron involvement (spasticity affecting the legs and upper limbs)
- Variably lower motor neuron involvement (muscle atrophy and sensory disturbances)
- Later pseudobulbar involvement including speech
- Preservation of cognitive function

Electrophysiologic Findings

Table 1 shows the results of various electrophysiologic studies in the different phenotypes of *ALS2*-related disorders. Note that nerve conduction velocities, visual evoked potentials, and brain stem auditory evoked potentials are normal in all phenotypes.

Table 1. Electrophysiologic Studies in *ALS2*-Related Disorder by Phenotype

Study	Phenotype		
	IAHSP	JPLS	JALS
MEP	Severe dysfunction of the corticospinal tracts [1]	NA	Absent or ↓ action potential, suggesting dysfunction of corticospinal tracts [2]
SSEP	Normal in early stages; abnormal in later stages	Poorly configured; normal central conduction	NA
EMG	No signs of denervation	No signs of denervation	Signs of denervation
TCMS		No motor evoked potentials	

EMG = electromyography; IAHSP = infantile-onset ascending hereditary spastic paralysis; JALS = juvenile amyotrophic lateral sclerosis; JPLS = juvenile primary lateral sclerosis; MEP = motor evoked potentials; NA = not available; SSEP = somatosensory evoked potentials; TCMS = transcranial magnetic stimulation

1. Primitive, pure degeneration of the upper motor neurons

2. Kress et al [2005]

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].

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *ALS2*-related disorder **is established** in a proband with suggestive findings and biallelic pathogenic variants in *ALS2* identified on molecular genetic testing (see Table 2).

Note: Identification of biallelic *ALS2* variants of uncertain significance – or identification of one known *ALS2* pathogenic variant and one *ALS2* variant of uncertain significance – does not establish or rule out a diagnosis of this disorder.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be

diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *ALS2*-related disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ALS2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications. 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.

An amyotrophic lateral sclerosis (ALS) multigene panel that includes *ALS2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **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.

Table 2. Molecular Genetic Testing Used in *ALS2*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ALS2	Sequence analysis [3]	All sequence variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
5. 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.
6. 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 phenotypes on a clinical continuum ranging from infantile ascending hereditary spastic paraplegia (IAHSP) to juvenile forms without lower motor neuron involvement (juvenile primary lateral sclerosis [JPLS]) or with lower motor neuron involvement (juvenile amyotrophic lateral sclerosis [JALS]).

An increasing number of individuals have been identified with biallelic pathogenic variants in *ALS2* [Hadano et a 2001, Yang et al 2001, Eymard-Pierre et al 2002, Devon et al 2003, Gros-Louis et al 2003, Kress et al 2005, Eymard-Pierre et al 2006, Panzeri et al 2006, Sztriha et al 2008, Verschuuren-Bemelmans et al 2008, Herzfeld et al 2009, Mintchev et al 2009, Shirakawa et al 2009, Sheerin et al 2014, Simone et al 2018, Borg et al 2021, Lin et al 2021, Nogueira et al 2021, Shepheard et al 2021, Sprute et al 2021]. The following description of the phenotypic features associated with this disorder is based on these reports. Sprute et al [2021] reviewed the clinical and genetic characteristics of 82 individuals described in the literature to July 2020. There may be intra- as well as interfamilial phenotypic variability in *ALS2*-related disorder [Nogueira et al 2021].

Infantile ascending hereditary spastic paraplegia (IAHSP). Spasticity with increased reflexes and sustained clonus of the lower limbs begins during the first two years of life (and often in the first year) and extends to upper limbs by age seven to eight years. 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 in the advanced stage of disease are reported to require feeding by gastrostomy tube and to lose bladder and sphincter functions [Verschuuren-Bemelmans et al 2008].

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

Juvenile primary lateral sclerosis (JPLS) is characterized by 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].

Juvenile amyotrophic lateral sclerosis (JALS or ALS2). Onset is between ages three and 20 years. All affected show a spastic pseudobulbar syndrome (spasticity of speech and swallowing) together with spastic paraplegia. Peroneal muscular atrophy is observed in some (not all) individuals. At the time of the description of clinical manifestations, three individuals from one family were bedridden by ages 12, 20, and 50 years; another individual remained ambulatory until age 50 years [Ben Hamida et al 1990, Hentati et al 1994].

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

Genotype-Phenotype Correlations

Sprute et al [2021] identified significant clinical heterogeneity, and no correlation between disease severity and affected domain or type of variant. Both IAHSP and JPLS have been associated with truncating *ALS2* variants.

Nomenclature

In some instances, the same entity may be referred to as either juvenile primary lateral sclerosis (JPLS) or infantile ascending hereditary spastic paraplegia (IAHSP).

JALS may also be referred to as JALS/ALS2.

Prevalence

No data on prevalence are available; however, *ALS2*-related disorder is probably currently underdiagnosed.

ALS2-related disorder has 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 germline biallelic 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 that only four of 11 families with IAHSP have *ALS2* pathogenic variants. No other genes/loci causing this phenotype have been identified.

Autosomal recessive hereditary spastic paraplegia (ARHSP). In general in ARHSP with onset during the first decade, the progression is less severe and may appear non-progressive, and spasticity predominates over weakness. In later-onset ARHSP there may be progressive worsening of gait. Pseudobulbar involvement in *ALS2*-related disorder delineates it from other genetic forms of spastic paraparesis.

ARHSP caused by pathogenic variants in *ERLIN2* (SPG18; see Hereditary Spastic Paraplegia Overview) has been described in a consanguineous family from Saudi Arabia having four sibs with infantile-onset primary lateral sclerosis (PLS) with severe progression requiring wheelchair by age 12 years and associated with a homozygous splice junction pathogenic variant (c.499-1G>T).

Metabolic causes of progressive HSP include X-linked adrenoleukodystrophy, arylsulfatase A deficiency, and mitochondrial dysfunction (see Mitochondrial Disorders Overview); however, decline in behavior or cognitive function is frequently observed in these conditions.

Note: PLS, 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, has been reported in adults with an isolated degenerative process of the upper motor neurons. Phenotypic overlap has not been described between PLS and *ALS2*-related disorder [Brugman et al 2007].

Amyotrophic Lateral Sclerosis (ALS)

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

Management

No clinical practice guidelines specifically for *ALS2*-related disorder have been published. Management is similar to that of persons with the wider range of amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), and other neurodegenerative conditions.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ALS2*-related disorder, 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 *ALS2*-related Disorder

System/Concern	Evaluation	Comment
Neurologic	By an experienced neurologist	For evidence of UMN, LMN, & cranial nerve involvement
Developmental assessment		To incl: • Motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Scoliosis / Hip dislocation	By experienced orthopedist	
Musculoskeletal/ ADL	Physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Dysarthria	By speech & language therapist	Consider need for alternative communication.
Dysphagia	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in those w/ dysphagia &/or aspiration risk.
Oculomotor involvement	Ophthalmologic exam	Incl assessment of ocular movements
Bladder dysfunction	Urologist	Assess for bladder spasticity w/frequency & urgency of micturition.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Bowel dysfunction	Gastroenterologist	Assess for signs & symptoms related to immobility.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *ALS2*-related disorder to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community resources, ALS/MND support organizations, &/or family support organizations such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	Involvement of teams experienced in pediatric & neurologic neurodegenerative conditions

ADL = activities of daily living; LMN = lower motor neuron; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron

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

Treatment of Manifestations

Management by multidisciplinary specialists, including neurology, orthopedics, physical therapy, occupational therapy, speech and language therapy, and feeding specialists (gastroenterology, nutrition) is recommended.

Table 4. Treatment of Manifestations in Individuals with *ALS2*-related Disorder

Manifestation/Concern	Treatment	Considerations/Other
UMN involvement (spasticity) / LMN involvement (weakness)	Orthopedics / physical medicine & rehab / PT/OT	• Stretching to help avoid contractures & fractures • Consider need for orthotics, positioning & mobility devices (e.g., motorized chairs), & disability parking placard.
Developmental/ educational issues	See Developmental/Educational Management Issues.	
Scoliosis/hip dislocation	Per treating orthopedist	
Musculoskeletal/ADL	PT & OT to promote mobility & independence	
Dysarthria	Speech & language therapy	Use of computer technologies & devices adapted to facilitate writing & voice communication
Dysphagia	Gastrostomy tube placement may be required for persistent feeding issues.	Dietary supplements as needed to maintain weight
Bladder dysfunction	Antispasticity medications, catheter	Per routine management of spastic bladder
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family support/ resources	• Ensure appropriate social work involvement to connect families with local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	

ADL = activities of daily living; LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; UMN = upper motor neuron

Developmental/Educational Management Issues

The following information represents typical management recommendations for individuals with developmental / intellectual educational issues in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, and modified assignments.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated disabilities.

- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 5. Recommended Surveillance for Individuals with *ALS2*-related Disorder

System/Concern	Evaluation	Frequency
Neurologic involvement	Neurologic exam to monitor progression of existing findings & development of new findings	Annually or as needed
Development / Educational issues	Monitor developmental progress/educational needs.	
Spine and hips	Monitor to assure early detection of scoliosis &/or hip dislocation.	
Musculoskeletal/ ADL	PT & OT to monitor gross motor & fine motor skills & therapy/equipment needs	
Dysarthria	Per speech & language therapist	
Dysphagia	Monitor nutrition, safety of oral feeding in those w/o gastrostomy tube.	
Bladder dysfunction	Per treating urologist	
Bowel dysfunction	Per treating clinician	
Family support/ resources	Use of local resources, coordination of care	

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

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

ALS2-related disorder is 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., presumed to be carriers of one *ALS2* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ALS2* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *ALS2* pathogenic variant, each sib of an affected individual has at conception 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.
- Intrafamilial variability is recognized. For example, Mintchev et al [2009] describe two sibs with juvenile primary lateral sclerosis and homozygous *ALS2* c.2980-2A>G pathogenic variants; one sib required a wheelchair at age two years while the other sib required a wheelchair at age 50 years.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with *ALS2*-related disorder 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 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 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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ALS2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **MedlinePlus**
  Infantile-onset ascending hereditary spastic paralysis
- **MedlinePlus**
  Juvenile primary lateral sclerosis
- **ALS Association**
  Phone: 800-782-4747
  Email: alsinfo@alsa-national.org
  www.alsa.org
- **Amyotrophic Lateral Sclerosis Society of Canada**
  Canada
  Phone: 800-267-4257 (toll-free); 416-497-2267
  Email: communityservices@als.ca
  www.als.ca
- **MedlinePlus**
  Amyotrophic lateral sclerosis
- **Motor Neurone Disease Association**
  United Kingdom
  Phone: 01604 250505
  Fax: 01604 624726/638289
  Email: enquiries@mndassociation.org
  www.mndassociation.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Hereditary Spastic Paraplegia Information Page
- **Spastic Paraplegia Foundation, Inc.**
  Phone: 877-773-4483
  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 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ALS2	2q33.1	Alsin	alsod/ALS2 genetic mutations ALS2 database	ALS2	ALS2

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 ALS2-Related Disorder (View All in OMIM)

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

Molecular Pathogenesis

Biallelic pathogenic variants of *ALS2,* the gene encoding alsin Rho guanine nucleotide exchange factor, cause an early-onset progressive neurodegeneration, predominantly of upper motor neurons. This manifests clinically as *ALS2*-related disorder comprising the spectrum of IAHSP (infantile-onset ascending hereditary spastic paralysis), JALS (juvenile amyotrophic lateral sclerosis), and JPLS (juvenile primary lateral sclerosis). Alsin has multiple cellular functions including modulation of endosome and mitochondrial trafficking, and endocytosis.

Mechanism of disease causation. Nonsense, frameshift, missense, and splice site *ALS2* variants cause loss of function or dysfunction of the cellular processes.

Chapter Notes

Author Notes

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Revision History

- 13 May 2021 (bp) Comprehensive update posted live
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- 16 December 2004 (esb) Original submission

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