ALS2-Related Disorders

[Includes: Autosomal Recessive Juvenile Amyotrophic Lateral Sclerosis, Infantile-Onset Ascending Hereditary Spastic Paralysis, Juvenile Primary Lateral Sclerosis]

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About the Authors

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Summary

Disease 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 or JPLS) to forms with lower motor neuron involvement (autosomal recessive juvenile amyotrophic lateral sclerosis or 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 is 6.5 years), spasticity of facial muscles, uncontrolled laughter, spastic dystarthria, spastic gait, inconstant moderate muscle atrophy, bladder dysfunction, and sensory disturbances; some individuals are bedridden by age 12 to 50 years.

Diagnosis/testing. Results of electrophysiologic studies in ALS2-related disorders vary by phenotype; MRI shows brain changes in older individuals with IAHSP. Mutations in the ALS2 gene have been found in four of 11 families with IAHSP; other genes/loci have not been identified. Molecular genetic testing of ALS2 (KIAA1563), the only gene known to be associated with these disorders, detects mutations in all individuals with ALS2-related disorders and is available on a clinical basis.

Management. Treatment of ALS2-related disorders includes physical and occupational therapy to promote mobility and independence and use of computer technologies and devices to facilitate writing and voice communication. In one person, intrathecal baclofen improved spasticity. Early detection and treatment of hip dislocation and/or spine deformities prevent further complications. Surveillance includes 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. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband. Prenatal diagnosis for pregnancies at increased risk is possible if both disease-causing alleles of an affected family member have been identified.
Clinical Diagnosis

ALS2-related disorders involve retrograde degeneration of the upper motor neurons of the pyramidal tracts and comprise a clinical continuum from (1) infantile ascending hereditary spastic paraplegia (IAHSP)* to (2) juvenile forms without lower motor neuron involvement (juvenile primary lateral sclerosis or JPLS)* to (3) 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.

**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 is 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
- Inconstant and 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 Studies

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

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>IAHSP</th>
<th>JPLS</th>
<th>JALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEP 1</td>
<td>Severe dysfunction of the corticospinal tracts 2</td>
<td>NA 3</td>
<td>NA 3</td>
</tr>
<tr>
<td>SSEP 4</td>
<td>Normal in early stages; abnormal in later stages</td>
<td>Poorly configured; normal central conduction</td>
<td>NA 3</td>
</tr>
<tr>
<td>EMG 5</td>
<td>No signs of denervation</td>
<td>No signs of denervation</td>
<td>Signs of denervation</td>
</tr>
<tr>
<td>NCV 6</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>VEP 7</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>BAER 8</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCMS 9</td>
<td>No motor-evoked potentials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Motor-evoked potentials
2. Primitive, pure degeneration of the upper motor neurons
3. Not available
4. Somatosensory-evoked potentials
5. Electromyography
6. Nerve conduction velocities  
7. Visual-evoked potentials  
8. Brainstem auditory-evoked potentials  
9. Transcranial magnetic stimulation

**Neuroimaging Studies**

**IAHSP.** Magnetic resonance imaging (MRI) is normal in children. Older individuals have (1) brain cortical atrophy predominant in the motor areas; and (2) T2-weighted bilateral punctate hyperintense signals in the corticospinal pathways of the posterior arms of the internal capsule and brainstem. In addition, it is common to find T2- 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.** No information from neuroimaging studies is available.

**Testing**

Detection of the protein alsin using specific antibodies in protein extracts from skin biopsy fibroblasts is available on a research basis only.

**Molecular Genetic Testing**

_GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work; listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information._

**Gene.** _ALS2 (KIAA1563)_ is the only gene known to be associated with _ALS2_-related disorders.

**Other loci.** Mutations in the _ALS2_ gene have been found in only four of 11 families with IAHSP [Lesca et al 2003]; however, other genes/loci have not yet been identified.

**Molecular genetic testing: Clinical uses**

- **Diagnostic testing**
- **Carrier testing**
- **Prenatal diagnosis**

**Molecular genetic testing: Clinical method**

- **Sequence analysis** of the _ALS2_ exons from genomic DNA extracted from lymphocytes detects mutations in all individuals with _ALS2_-related disorders.

  Note: Because _ALS2_-related disorders are defined by the presence of a mutation in _ALS2_, the mutation detection rate is 100%.

**Molecular genetic testing: Research**

- **Sequence analysis** of alsin cDNA obtained from an RNA extract of lymphoblastoid cell lines and/or fibroblasts is performed on a research basis only.

Table 2 summarizes molecular genetic testing for this disorder.

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Mutation Detection Rate</th>
<th>Test Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence analysis</td>
<td><em>ALS2</em> truncating and nonsense mutations in the coding or splice site regions</td>
<td>100% ¹</td>
<td>Clinical [Testing]</td>
</tr>
</tbody>
</table>

¹. Because _ALS2_-related disorders are defined by the presence of a mutation in _ALS2_, the mutation detection rate is 100%.

**Interpretation of test results.** For issues to consider in interpretation of sequence analysis results, click [here](http://www.genetests.org/servlet/access?id=8888891&key=gu6guoJIQ...).

**Genetically Related Disorders**
No other phenotypes are associated with mutations in ALS2.

**Clinical Description**

**Natural History**

Mutations 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 age. 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 are now in their 30s have neither experienced recurrent bronchopneumonia nor required feeding gastrostomy.

Overall, IAHSP is compatible with long survival. Mental status is preserved.

**Juvenile primary lateral sclerosis (JPLS).** Examination reveals upper motor neuron findings of pseudobulbar palsy and spastic quadriplegia, without dementia, 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 on their own, while others walk in time but lose the ability to walk independently by the first decade of life. Speech deterioration starts between two years and ten years of age, and no cognitive deterioration is reported.

**Autosomal recessive juvenile amyotrophic lateral sclerosis (JALS or ALS2)** [Ben Hamida et al 1990, Hentati et al 1994]. Affected individuals have onset between three and 20 years of age and constantly show a spastic pseudobulbar syndrome together with spastic paraplegia. Peroneal muscular atrophy was observed in some, but not all, individuals. No atrophy or fasciculation of the tongue was found. At the time of the description of clinical symptoms, three individuals from one family were bedridden by the ages of 12, 20, and 50 years.

**Genotype-Phenotype Correlations**

So far, the IAHSP and JPLS phenotypes are uniform among individuals from nine families with truncating ALS2 mutations. Table 3 summarizes the eight mutations from nine families classified as IAHSP or JPLS and some sibs of the tenth family classified as JALS. Nine out of ten families with mutations in ALS2 show a uniform clinical course, while the Tunisian family with juvenile amyotrophic lateral sclerosis has a relatively milder phenotype.
Table 3. Clinical Features of Individuals with ALS2-Related Disorders by ALS2 Mutation

<table>
<thead>
<tr>
<th>Mutation</th>
<th>A46fs</th>
<th>I336fs</th>
<th>T475fs</th>
<th>V491fs</th>
<th>L623fs</th>
<th>N846fs</th>
<th>R998st</th>
<th>M1207st</th>
<th>V1574fs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Mutant Protein</td>
<td>49</td>
<td>339</td>
<td>545</td>
<td>492</td>
<td>645</td>
<td>857</td>
<td>997</td>
<td>1206</td>
<td>1616</td>
</tr>
<tr>
<td>Phenotype</td>
<td>JALS</td>
<td>IAHSP</td>
<td>JPLS</td>
<td>IAHSP</td>
<td>JPLS</td>
<td>IAHSP</td>
<td>IAHSP</td>
<td>IAHSP</td>
<td>IAHSP</td>
</tr>
<tr>
<td>Onset (years)</td>
<td>3-10</td>
<td>1.5</td>
<td>1.2</td>
<td>1.5</td>
<td>1-2</td>
<td>1.4</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Loss of Walking (years)</td>
<td>12-50</td>
<td>4</td>
<td>NA 1</td>
<td>4</td>
<td>NA</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>Yes 2</td>
</tr>
<tr>
<td>Bulbar Symptoms (years)</td>
<td>Yes</td>
<td>13</td>
<td>4</td>
<td>8</td>
<td>2-10</td>
<td>12</td>
<td>3</td>
<td>13</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Upper/Lower Motor Neuron Involvement</td>
<td>Both 3</td>
<td>U 4</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

All reported disease-causing ALS2 mutations cause truncation of protein.

1. NA = walking never achieved
2. Age unknown
3. 50% of cases
4. Upper motor involvement

Penetration

All individuals who are homozygous or compound heterozygous for ALS2 mutations manifest the disease.

Anticipation

Anticipation has not been observed.

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.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —Ed.


Hereditary spastic paraplegia is characterized by insidiously progressive lower extremity weakness and spasticity. HSP is classified as "uncomplicated" or "pure" if neurologic impairment is limited to progressive lower extremity spastic weakness, hypertonic urinary bladder disturbance, mild diminution of lower extremity vibration sensation and, occasionally, joint position sensation. HSP is classified as "complicated" ("complex") if the impairment present in uncomplicated HSP is accompanied by other system involvement or other neurologic findings such as seizures, dementia, amyotrophy, extrapyramidal disturbance, or peripheral neuropathy in the absence of other disorders such as diabetes mellitus.

Hereditary spastic paraplegia may be transmitted in an autosomal dominant manner, an autosomal recessive...
manner, or an \textit{X}-linked recessive manner. (The mode of inheritance is usually established by family history and rarely with molecular genetic testing.) In \textit{autosomal dominant} hereditary spastic paraplegia (ADHSP) \textit{intrafamilial variability} in the age at onset is common. Progressive spasticity and motor disability involving the upper limbs, oculomotor function, and bulbar function are rarely observed in any of the different genetic forms of hereditary spastic paraplegia.

Children with ADHSP and with congenital onset of spasticity (mutations in the genes encoding spastin and 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.

\textbf{ARHSP.} In general, in \textit{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 \textit{ALS2} mutations in ARHSP has not yet been investigated.

Normal brain white matter on MRI rules out the diagnosis of leukodystrophy.

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

\textbf{Primary lateral sclerosis (PLS).} 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 \textit{isolated} degenerative process of the upper motor neurons, with sporadic occurrence [Pringle et al 1992]. However, the role of \textit{ALS2} mutations in adult- or adolescent-onset forms of primary lateral sclerosis has not been yet investigated.

\textbf{Amyotrophic lateral sclerosis (ALS).} See Amyotrophic Lateral Sclerosis Overview.

ALS is a progressive neurodegenerative disease involving both the upper motor neuron (UMN) and lower motor neuron (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 topographical representation.

\textbf{ALS1.} Approximately 20\% of individuals with familial ALS have ALS1 with an identified disease-causing mutation in \textit{SOD1}. About 3\% of affected individuals with no family history of ALS have \textit{SOD1} mutations. Inheritance of ALS1 is \textit{autosomal dominant}.

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

The role of \textit{ALS2} mutations among the common adult forms of ALS was investigated by the following:

- Hand et al (2003), who screened for mutations in \textit{ALS2} from 95 unrelated individuals with familial ALS, 95 unrelated individuals with simplex ALS (i.e., only one individual affected in the family), and 11 individuals with early-onset amyotrophic lateral sclerosis. All 34 exons of \textit{ALS2} plus the 5’ and 3’ untranslated regions were sequenced and no disease-associated mutations were found. Each of the 23 variants identified was also analyzed among controls. No mutation of \textit{ALS2} has been identified as a cause of adult-onset familial or simplex ALS.

- Nagano et al (2003), who evaluated three Japanese individuals with autosomal recessive ALS. Although single nucleotide polymorphisms (SNPs) were identified in non-coding regions of \textit{ALS2}, no disease-causing mutations were identified. The possibility remains that the identified SNPs might predispose to ALS.

\section*{Management}

\subsection*{Evaluations at Initial Diagnosis to Establish the Extent of Disease}

- Family history
- Neurologic exam, including assessment of eye movements, speech, fine motor and gross motor function, swallowing

\subsection*{Treatment of Manifestations}

- Physical and occupational therapy to promote mobility and independence
- Use of computer technologies and devices adapted to facilitate writing and voice communication
- Intrathecal baclofen in one person improved spasticity, which facilitated care but did not improve motor
function.

Prevention of Secondary Complications

- Early detection and treatment of hip dislocation and/or spine deformities

Surveillance

- Evaluation for feeding difficulties and modification of diet to reduce risk of aspiration

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

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 and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

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.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

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.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks’ gestation or chorionic villus sampling (CVS) at about 10-12 weeks’ gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.
Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —Ed.

### Molecular Genetics of ALS2-Related Disorders

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Chromosomal Locus</th>
<th>Protein Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS2</td>
<td>2q33</td>
<td>Alsin</td>
</tr>
</tbody>
</table>

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

### OMIM Entries for ALS2-Related Disorders

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

### Genomic Databases for ALS2-Related Disorders

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Entrez Gene</th>
<th>HGMD</th>
<th>GeneCards</th>
<th>GDB</th>
<th>GenAtlas</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS2</td>
<td>606352</td>
<td>135696</td>
<td>ALS2</td>
<td>135696</td>
<td>ALS2</td>
</tr>
</tbody>
</table>

For a description of the genomic databases listed, click here.

**Normal allelic variants:** ALS2 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.


**Normal gene product:** Sequence comparisons suggest that ALS2 encodes a protein containing 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)]. The activity of a GEF activates one or more small GTPases, facilitating the releasing of GDP and exchange for GTP. Alsin, the protein encoded by ALS2, has been shown to be capable of acting as a GEF for Rab5, a GTPase implicated in endosomal trafficking [Otomo et al 2003]. When highly expressed, alsin has also been shown to act on Rac1, a G protein involved in actin cytoskeleton remodeling [Topp et al 2004].

Endogenous alsin is enriched in nervous tissue where it is peripherally bound to the cytoplasmic face of endosomal membranes. This association requires the amino-terminal "RCC1-like" GEF domain [Yamanaka et al 2003], but C-terminal sequences are also required [Otomo 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.

Ectopically expressed alsin co-localizes with Rab5 and the early endosome antigen-1 (EEA1) onto early endosomal compartments and stimulates the enlargement of endosomes in cultured cortical neurons and non-neuronal cells in a Rab5-GEF activity-dependent manner [Otomo et al 2003]. Essentially, full-length ALS2 including the amino-terminal RLD domain is required for proper membrane targeting of alsin [Yamanaka et al 2003].

Exogenously expressed ALS2 forms a homophilic oligomer through its C-terminal regions, which carries a VPS9 domain; oligomerization of ALS2 is apparently crucial for Rab5-GEF activity in vitro and ALS2-mediated endosome enlargement in cells [Kunita et al 2004].
A gene homologous to ALS2, named ALS2 C-terminal like (ALS2CL), resides on chromosome 3p21, and encodes a 108-kd protein [Hadano et al. 2004]. ALS2CL could be a novel factor modulating the Rab5-mediated endosome dynamics in the cells.

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

A feature common to all reported ALS2 mutations causing motor neuron diseases is a loss of protein stability [Yamanaka et al. 2003], which leads to reduction or loss of all three potential GEF domains. Most current work is focusing on the role of ALS2 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 ALS2 in the death of upper motor neurons beginning in early postnatal life.

**Resources**

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -Ed.

- **Amyotrophic Lateral Sclerosis Association (ALSA)**
  27001 Agoura Road, Suite 150
  Calabasas Hills, CA 91301-5104
  **Phone:** 800-782-4747 (patient hotline); 818-880-8007; 818-340-7573 (TDD)
  **Fax:** 818-880-9006
  **Email:** alsinfo@alsa-national.org
  www.alsa.org

- **Amyotrophic Lateral Sclerosis Society of Canada**
  265 Yorkland Blvd, #300
  Toronto, Ontario, Canada M2J 1S5
  **Phone:** 888-267-4ALS (888-267-4257); 416-497-2267
  **Fax:** 416-497-1256
  **Email:** SI@als.ca
  www.als.ca

- **National Ataxia Foundation**
  2600 Fernbrook Lane; Suite 119
  Minneapolis, MN 55447
  **Phone:** 763-553-0020
  **Fax:** 763-553-0167
  **Email:** naf@ataxia.org
  www.ataxia.org

- **National Institute of Neurological Disorders and Stroke**
  Hereditary Spastic Paraplegia

- **Spastic Paraplegia Foundation, Inc.**
  209 Park Rd.
  Chelmsford, MA 01824
  **Phone:** 703-495-9261
  **Email:** community@sp-foundation.org
  sp-foundation.org

**Resources Printable Copy**

**References**

[PubMed]

Published Statements and Policies Regarding Genetic Testing
No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited


Suggested Readings


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