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Amyotrophic Lateral Sclerosis Overview

[*Lou Gehrig's Disease*]

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Summary

Disease characteristics. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease involving both the upper motor neurons (UMN) and lower motor neurons (LMN). UMN signs include hyperreflexia, extensor plantar response, increased muscle tone, and weakness in a topographical representation. LMN signs include weakness, muscle wasting, hyporeflexia, muscle cramps, and fasciculations. In the early stage of the disease, the clinical aspects of ALS can vary. Affected individuals typically present with asymmetric focal weakness of the extremities (stumbling or poor handgrip) or bulbar findings (dysarthria, dysphagia). Other findings include muscle fasciculations, muscle cramps, and lability of affect but not necessarily mood. Regardless of initial symptoms, atrophy and weakness eventually affect other muscles. The mean age of onset of ALS in individuals with no known family history is 56 years and in individuals with more than one affected family member (familial ALS or FALS) is age 46 years. In sporadic ALS, more men are affected than women and men may have an earlier disease onset. Average duration of the disease is about three years but can vary significantly. Death usually results from compromise of the respiratory muscles.

Diagnosis/testing. The diagnosis of ALS is based on clinical features, electrodiagnostic testing (EMG), and exclusion of other health conditions with related symptoms. Pathologically, a definitive diagnosis of ALS can be made based on brainstem and spinal cord findings. Once the diagnosis of ALS has been established in an individual, molecular genetic testing of the *SOD1* gene can be used in individuals with a positive or incomplete family history to establish a specific diagnosis and to clarify mode of inheritance for genetic counseling purposes. Such testing is clinically available. Approximately 20% of individuals with familial ALS have ALS1 with an identified disease-causing mutation in *SOD1*. About three percent of affected individuals with no family history of ALS have *SOD1* mutations.

Management. Treatment is palliative and many individuals with ALS benefit from care by a multidisciplinary team including a neurologist, specially trained nurses, pulmonologist, speech

therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetics professional. Riluzole is the only currently FDA-approved drug for treatment of ALS. Oral secretions in individuals with bulbar symptoms can be reduced with tricylic antidepressants and anticholinergic agents. Pseudobulbar affect can be managed with antidepressants. Swallowing difficulties can be alleviated by thickening liquids and pureeing solid food, and eventually by use of a gastrostomy tube to help maintain caloric intake and hydration. Medications such as baclofen and benzodiazepines can help relieve spasticity and muscle cramps. Alphabet boards and computer-assisted devices can aid communication. Other assistance devices such as walkers, wheelchairs, bathroom modifications, hospital beds, and hoyer lifts can aid in activities of daily life. Ventilatory assistance may include BIPAP. Hospice care in terminal stages is beneficial.

Genetic counseling. Amyotrophic lateral sclerosis can be inherited in an autosomal dominant, autosomal recessive, or X-linked dominant manner. Recurrence risk depends on the certainty with which the mode of inheritance can be established in a family. ALS1 caused by mutations in the *SOD1* gene is typically inherited in an autosomal dominant manner. Most individuals diagnosed as having ALS1 have an affected parent or other first-degree relative; however, the *de novo* mutation rate is not known and penetrance is incomplete. If a disease-causing mutation in the *SOD1*, *ALS2*, *SETX*, or *VAPB* gene has been identified in an affected family member, prenatal testing is possible for pregnancies at increased risk. However, requests for prenatal diagnosis of this adult-onset disease are uncommon and controversial and therefore require careful genetic counseling.

Definition

Clinical Manifestations of ALS

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease involving both upper motor neurons (UMNs) and lower motor neurons (LMNs).

Upper motor neurons , located in the motor cortex of the frontal lobe, send their axons through the great corticofugal tracts to the brainstem (corticobulbar neurons) and the spinal cord (corticospinal neurons) and influence patterned activity of the lower motor neurons (LMS). Additional UMN influences on the LMN are carried over descending pathways of the brainstem. UMN signs include hyperreflexia, extensor plantar response, and increased muscle tone.

Lower motor neurons , located in the brainstem and spinal cord, innervate striated muscle. LMN signs include weakness, muscle wasting, hyporeflexia, muscle cramps, and fasciculations.

Disease characteristics. In the early stage of the disease, the clinical aspects of ALS are variable. Affected individuals typically present with asymmetric focal weakness of the extremities (stumbling or poor handgrip) or bulbar findings (dysarthria, dysphagia). Other findings include muscle fasciculations, muscle cramps, and lability of affect but not necessarily mood. A diagnostic feature of ALS, unusual in other disorders, is the presence of hyperreflexia in segmental regions of muscle atrophy, unaccompanied by sensory disturbance.

At presentation, limb involvement occurs more often than bulbar involvement. Onset in the lower extremities is most common for familial ALS [Mulder et al 1986, Siddique 1991]. Depending on the topography of weakness, subtypes of ALS may be identified, including "progressive bulbar palsy" in individuals presenting with speech disturbance and swallowing difficulties; limb-onset ALS; progressive muscular atrophy; and UMN-predominant ALS. Regardless of initial symptoms, atrophy and weakness eventually affect other muscles.

The ocular muscles are resistant to degeneration in ALS, but may eventually be affected. This has been noted in individuals who choose tracheostomy and ventilatory support to extend their life span. As all muscles of communication and expression become paralyzed the individual is "locked-in." In some instances, eye movements may remain intact allowing communication by way of special devices.

Death usually results from compromise of the respiratory muscles.

Age of onset. "Sporadic" ALS (i.e., ALS occurring in individuals with no family history of ALS, or SALS) is distinguished from familial ALS (i.e., ALS occurring in individuals with more than one family member with ALS, or FALS). They are clinically similar; however, the mean age of onset of SALS is 56 years with the average duration being three years after onset of symptoms [Tandan & Bradley 1985, Ringel et al 1993, Testa et al 2004] and the mean age of onset of FALS is about 46 years [Juneja et al 1997].

Individuals younger than age 55 years at onset of symptoms survive longer, with no distinction based on gender [Magnus et al 2002]. Individuals who are diagnosed with ALS after age 80 years seem to survive 1.7 years less than those with onset before age 80 years [Forbes et al 2004]. Athough repiratory function declines faster in ALS with bulbar onset, overall muscle weakness declines more slowly [Magnus et al 2002]. Progression in familial ALS may be significantly shorter or longer than in sporadic ALS [Cudkowicz et al 1997, Juneja et al 1997].

Frontotemporal involvement. Frontotemporal dementia (FTD) is a profound alteration in personality and social conduct characterized by loss of volition and insight, social disinhibition, and distractibility, but with preservation of memory function [Neary et al 1998]. Other common features are cognitive deficits in the domains of attention, abstraction, planning, and problem-solving with preservation of perception and spatial functions. Language may be preferentially involved in individuals with progressive aphasia.

About five percent of individuals with ALS, regardless of family history, have frontotemporal dementia, which meets clinical criteria described by Neary et al (1998) [Hosler et al 2000]. In families with dominantly inherited ALS/FTD, one member may have either FTD or ALS or both conditions [Hosler et al 2000].

Thirty percent to 50% of individuals with ALS have executive function impairment, but do not meet the Neary criteria of dementia [Portet et al 2000, Lomen-Hoerth et al 2003]. In contrast to individuals with FTD, individuals with ALS may have more subtle difficulties with executive function that could be missed on routine mental status examination. Formal neuropsychological testing can identify subtle alterations, even though they are masked by socially favorable traits such as empathy and optimism. These favorable traits have been known to specialists dealing with ALS and lead to considerable bonding between health care givers and persons with ALS. Affected individuals are also generally well-liked by the family, as social connections are maintained and their 'positive' attitude is appreciated.

Conversely, in one study, 14% of individuals with FTD and no family history of ALS or FTD were identified on clinical examination as having ALS-like findings [Lomen-Hoerth et al 2002].

Deficits in verbal and nonverbal fluency and concept formation are not as severe as the executive function deficits that have been seen in individuals with ALS who do not have dementia; these cognitive deficits may appear early in the course of the disease [Schreiber et al 2005].

White matter structural abnormalities may be present in the frontal and temporal lobes of individuals with ALS who do not demonstrate evidence of cognitive change [Abrahams et al 2005].

Other. A male predominance of 1.3:1 has been noted in individuals with sporadic ALS.

Penetrance of familial ALS is age dependent. Fifty percent of individuals with a *SOD1* disease-causing gene mutation are symptomatic by age 46 years and 90% are symptomatic by age 70 years [Williams et al 1988, Siddique 1991]. However, these percentages are likely to be an overestimate for familial ALS because of ascertainment bias of the families with high penetrance.

Anticipation is not thought to be a feature, although intrafamilial and interfamilial variability in age of onset is not uncommon [Appelbaum et al 1992].

Establishing the Diagnosis of ALS

The diagnosis of ALS requires characteristic clinical features and findings on electrodiagnostic testing, as well as exclusion of other health conditions with related symptoms (see Differential Diagnosis).

Clinical features. The El Escorial criteria [Brooks et al 2000] established the requirements for diagnosis of ALS for enrollment of subjects in research studies. The clinical diagnosis, in practice, does not require such stringent criteria:

A The presence of:

- **1** Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic, or neuropathologic examination **AND**
- **2** Evidence of upper motor neuron (UMN) degeneration by clinical examination **AND**
- **3** Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, together **WITH**

B The absence of:

- **1** Electrophysiologic or pathologic evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, **AND**
- **2** Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs.

Clinical evidence of UMN and LMN signs in four regions of the central nervous system (CNS) [i.e., brainstem (bulbar cranial motor neurons) or cervical, thoracic, or lumbosacral spinal cord (anterior horn motor neurons)] can be obtained by a careful history and physical and neurologic examinations.

The clinical diagnosis of ALS, without pathologic confirmation, may be categorized into various levels of certainty by clinical and laboratory assessment based on the El Escorial criteria [Brooks et al 2000]:

- **Clinically definite ALS:** The presence of UMN and LMN signs in three regions
- **Clinically definite familial, laboratory-supported ALS:** ALS presenting with progressive upper and/or lower motor neuron signs in at least a single region (in the absence of another cause for the abnormal neurologic signs) with an identified

disease-causing mutation in the *SOD1* gene in the proband or a positive family history of an individual with an identified disease-causing mutation in the *SOD1* gene

- **Clinically probable ALS:** The presence of UMN signs and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs
- **Clinically probable, laboratory-supported ALS:** Clinical signs of UMN and LMN dysfunction are in only one region, or UMN signs alone present in one region, and LMN signs defined by EMG criteria present in at least two limbs
- **Clinically possible ALS:** Clinical signs of UMN and LMN dysfunction found together in only one region or UMN signs found alone in two or more regions; or LMN signs found rostral to UMN signs and in which the diagnosis of clinically probable, laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies
- **Clinically suspected ALS:** A pure LMN syndrome

Electrodiagnostic testing. Electromyogram (EMG) can demonstrate electrophysiologic evidence of LMN involvement in clinically affected or clinically uninvolved regions.

Pathology. A definitive diagnosis of ALS can be made based on brainstem and spinal cord pathology. Pathologic changes are: (1) degeneration and loss of the motor neurons in the anterior horns and in the motor nuclei of cranial nerves VII, X, and XI and most commonly the hypoglossal nucleus; and (2) axonal loss with decreased myelin staining in the lateral and anterior corticospinal tracts. Degeneration of the corticobulbar and corticospinal tract is detected at the level of the internal capsule and cerebral peduncles in the midbrain. Some individuals show mild degeneration of the mid-zone of the posterior sensory tracts, although sensory loss is usually not apparent during life.

Loss of Betz cells in the motor cortex has been documented, but can be missed on account of paucity of Betz cells.

Histologic findings include presence of Lewy-like bodies and Bunina bodies in the cytoplasm of motor neurons. Ubiquinated bodies, described as skein-like inclusions, are virtually always present.

Differential Diagnosis of ALS

Other hereditary and acquired conditions to be considered when establishing the diagnosis of ALS are discussed below [Traynor et al 2000].

Hereditary disorders include the following:

- Spinal and bulbar muscular atrophy (SBMA, Kennedy disease) is an X-linked recessive disorder, typically occurring in males only, characterized by proximal muscle weakness or muscle atrophy, and fasciculations. Affected males often show gynecomastia, testicular atrophy, and reduced fertility as a result of androgen insensitivity. SBMA can be distinguished clinically from non-familial ALS by the lack of upper motor neuron involvement, slow course, gynecomastia, and sensory involvement. Molecular genetic testing of the androgen receptor *(AR)* gene is diagnostic.
- Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by progressive degeneration and loss of the anterior horn cells in the spinal cord and in some brain stem nuclei, resulting in proximal greater than distal symmetric muscle

weakness and atrophy (LMN involvement only). The onset of weakness ranges from before birth to adulthood. Molecular genetic testing of the *SMN* gene identifies most, but not all, individuals with spinal muscular atrophy caused by mutations in the *SMN* gene. ALS8 (also known as SMAIV or Finkel type SMA) could be considered in the context of a negative *SMN* gene test in an individual with adult-onset LMN disease with some UMN involvement. ALS8 is caused by mutations in *VAPB* and inherited in an autosomal dominant manner.

- Mutations in the gene encoding dynactin have been observed in an early-adulthood-onset, slowly progressive autosomal dominant lower motor neuron disease with vocal cord involvement, but normal sensation [Puls et al 2003].
- Primary lateral sclerosis (PLS) refers to 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. Controversy exists as to whether PLS is a separate disorder, in upper motor neuron predominant ALS, or in progressive ascending paralysis noted in infants that starts as spastic paraparesis and culminates in PLS [Strong & Gordon 2005]. Mutations in at least one gene *(ALS2)* are associated with both ALS and PLS (see Autosomal Recessive ALS).
- Hereditary spastic paraplegia (HSP) is characterized by insidiously progressive lower extremity weakness and spasticity. HSP is classified as "uncomplicated" 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" if the impairments present in uncomplicated HSP are accompanied by other system involvement or other neurologic findings such as seizures, dementia, amyotrophy, extrapyramidal disturbance, or peripheral neuropathy. Nonsyndromic or pure HSP does not reduce life span. HSP can be inherited in an autosomal dominant, autosomal recessive, or X-linked recessive manner. HSP is genetically heterogeneous, with at least 11 genes identified and at least 30 loci mapped.
- Hexosaminadase A deficiency results in a group of neurodegenerative disorders caused by intralysosomal storage of the specific glycosphingolipid GM2 ganglioside. The juvenile, chronic, and adult-onset variants of hexosaminidase A deficiency are slowly progressive and have variable neurologic findings, including progressive dystonia, spinocerebellar degeneration, motor neuron disease, and, in some individuals with adult-onset disease, a bipolar form of psychosis.
- Adult polyglucosan disease is a slowly progressive disease of UMN and LMN dysfunction with distal sensory loss, early neurogenic bladder, cerebellar dysfunction, and cognitive impairment with onset after age 40 years [Tonin et al 1992, McDonald et al 1993]. Adult polyglucosan disease is autosomal recessive and caused by mutations in the gene encoding the glycogen branching enzyme.

Acquired disorders include cervical spine disease, brain stem or spinal cord tumors, thyroid disorders, lead poisoning, vitamin B12 deficiency, multiple sclerosis, paraneoplastic syndrome with occult cancer, motor neuropathies, myasthenia gravis, myasthenic syndrome, and inclusion body myositis.

Cervical spondylosis with cervical stenosis causing UMN signs in the legs and LMN signs in the arms should be considered as a differential diagnosis. Because cervical spondylosis is common, it is often identified in individuals who also have ALS. Electromyogram (EMG) and nerve conduction velocity (NCV) testing are performed to establish clinical evidence and extent of LMN disease.

To evaluate for other health conditions with related symptoms, the following may be performed:

- Neuroimaging of brain and/or spinal cord
- Blood studies, such as CBC; serum concentration of vitamin B12, lead, and TSH; and GM_1 ganglioside autoantibodies (sometimes elevated in autoimmune motor neuropathies) [Lange et al 1992]
- CSF examination, to evaluate for chronic infectious diseases or multiple sclerosis
- Serum neuronal autoantibodies for paraneoplastic syndromes associated with occult cancer
- Muscle and/or nerve biopsy, as indicated
- Testing for heavy metals if exposure is suspected

Prevalence of ALS

The number of individuals newly diagnosed with ALS each year is 1-3:100,000. The prevalence of individuals with ALS is roughly 4-8:100,000 [Annegers et al 1991, Chancellor & Warlow 1992, McGuire et al 1996, Traynor et al 1999] and is similar to the number of newly diagnosed individuals each year because people live only two to five years after the diagnosis of ALS is established.

Although the mean age of diagnosis is 56 years in sporadic ALS, individuals age 80 years and over have a standardized incidence of 10.2:100,000 in men and 6.1:100,000 in women [Forbes et al 2004].

Ethnic presentation of ALS worldwide is equal with the exception of the South Pacific where the incidence of an ALS/parkinsonism/dementia complex is higher [Zhang et al 1996, Plato et al 2002, Waring et al 2004]. Although recent studies suggest a lower incidence in African populations, those results remain to be verified by population-based prospective studies.

Causes

Environmental (Acquired) Causes of ALS

The environmental causes of ALS have been studied for many years. A multitude of environmental exposures have been proposed as possible contributors to the cause of ALS, including mercury, manganese, and farming (fertilizers, insecticides, herbicides), in addition to physical and dietary factors [Wicklund 2005].

Environmental exposures have been proposed as the explanation for an increased incidence of ALS in Gulf War veterans [Haley 2003, Horner et al 2003]. Further investigation is ongoing and a registry has been developed for veterans with ALS [Kasarkis et al 2004]. Of note, veterans with a diagnosis of ALS have been entitled to Veterans' Administration healthcare and disability benefits.

Heritable Causes

An estimated 10% of individuals with ALS have at least one other affected family member and are said to have familial ALS (FALS).

Familial ALS can be categorized by mode of inheritance and subcategorized by specific gene or chromosomal locus.

Autosomal Dominant ALS (see Table1)

Table 1. Molecular Genetics of Autosomal Dominant ALS

% of Individuals with Familial ALS	Locus Name	Disease Name	Gene Symbol	Chromosomal Locus	Protein Name	References
20%	ALS1	FALS	*SOD1*	21q22.1	Superoxide dismutase (Cu-Zn)	ALS Online Database [Rosen et al 1993, Deng et al 1993]
Rare	ALS3	FALS		18q21		Hand et al 2002
Rare	ALS4 [1]	Motor neuropathy with pyramidal features	*SETX*	9q34	Senataxin	Chance et al 1998, de Jonghe et al 2002, Chen et al 2004
Rare	ALS6	FALS		16q12		Abalkhail et al 2003, Ruddy et al 2003, Sapp et al 2003
Rare	ALS7	FALS		20ptel		Sapp et al 2003
Rare	ALS8 [1]	Finkel type SMA IV	*VAPB*	20a13.3	Vesicle-associated membrane protein-associated protein B/C	Nishimura et al 2004
Unknown	ALS/FTD [1]			9p21		Yan et al 2006
Rare	ALS/FTD [1]			17q		Wilhelmsen et al 2004
	SPG17 [1]	*BSCL2*-related neurologic disorders (Silver syndrome)	*BSCL2*	11q12-q14	Seipin	Windpassinger et al 2004
		IBMPFD [2]	*VCP*	9p21.1-p12	Valosin containing protein	Watts et al 2004

1. ALS-related motor neuron disorders with both UMN and LMN involvement
2. IBMPFD: Inclusion body myopathy associated with Paget disease of bone and/or frontotemporal dementia

ALS1. The *SOD1* gene is 12 kb in length with five exons and four introns. Over 100 mutations, predominantly missense, have been found throughout all five exons [Brown, unpublished communication; Gaudette et al 2000; ALS Online Database]. The exon 1 p.Ala4Val mutation accounts for about 50% of all mutations in North American families. Only four mutations have been detected in exon 3 [Andersen et al 1997, Boukaftane et al 1998, Shaw et al 1998, Segovia-Silvestre et al 2002, Andersen et al 2003].

SOD1 mutations account for only approximately 20% of all familial ALS and approximately three percent of sporadic ALS [Jackson et al 1997, Shaw et al 1998, Battistini et al 2005]. Simplex cases (i.e., those involving individuals with no family history of ALS) with *SOD1* mutations are most likely the result of incomplete penetrance or incomplete family history information [Suthers et al 1994], although *de novo* mutations, observed in one family with the H80R mutation [Alexander et al 2002], provide another explanation.

The SOD1 protein consists of 153 highly conserved amino acids with copper and zinc binding sites [Deng et al 1993]. SOD1 is a metalloenzyme that catalyzes the conversion of the superoxide anion to hydrogen peroxide and molecular oxygen. It is presumed to have a role in preventing oxidative damage to cells by reducing the free radicals [Cole & Siddique 1999]. Demetallated, reduced, and unfolded monomers of SOD1 that penetrate the mitochondria are oxidized and form aggregates via intermolecular covalent bonds. These detergent-resistant

aggregates are toxic and disrupt spatial order, resulting in mitochondrial failure. Wild-type SOD1 also participates in this process [Deng et al 2006, Furukawa et al 2006]. The dimers of intermolecular linked molecules of SOD1 may provide the seed on which a scaffolding of oligomers may form because of exposed hydrophobic domains, resulting in molecular tubes that may damage membranes. These observations thus provide an underpinning to the current understanding that *SOD1* mutations produce a toxic gain of function rather than an enzymatic deficiency. The toxic gain of function hypothesis was derived from the following observations:

- Dominant mutations are unlikely to cause enzyme deficiencies because of the presence of the compensatory allele, and a correlation between disease severity and the level of enzyme activity has not been established. For example, mutations with only marginally reduced enzyme activity, such as p.Asp90Ala and p.Gly93Asp, have been identified [Esteban et al 1994, Sjalander et al 1995].
- Knock-out mice, homozygous for *SOD1* deletions, are unaffected by motor neuron disease [Reaume et al 1996], while mice over-expressing human *SOD1* mutations develop motor neuron disease despite having higher SOD1 enzymatic activity than their non-transgenic littermates [Gurney et al 1994].

Age of onset of ALS1 is poorly correlated with genotype; intrafamilial variability can be extensive [Cudkowicz et al 1997, Juneja et al 1997]. While particular mutations have been reported to be associated with earlier age of onset, sample sizes are too small to draw generalizations. For example, Orrell et al (1997) reported a range of duration of 2.5-20 years in individuals with the p.Ile113Thr mutation and of 2-12 years in individuals with the p.Gly93Arg mutation. The p.Ala4Val mutation, present in approximately 50% of all North American families with identifiable *SOD1* mutations, is consistently associated with an average rapid disease course of one year [Juneja et al 1997]. On the opposite end of the spectrum are mutations that confer a significantly longer mean duration of at least 17 years, such as p.Gly37Arg, p.Gly41Asp, p.His46Arg, and p.Glu100Lys [Aoki et al 1993; Cudkowicz et al 1997; Juneja et al 1997; Siddique & Brooks, unpublished observation].

Reduced penetrance has been documented, most notably with the p.Ile113Thr and p.Asp90Ala mutations [Jones et al 1995, Orrell et al 1995, Khoris et al 2000].

Clinical presentation can occasionally be correlated with *SOD1* mutations. Symptomatic persons with p.Ala4Val and p.Val148 mutations often have few UMN findings, which has led to the El Escorial criterion that LMN findings and an *SOD1* mutation are sufficient to establish the diagnosis of ALS [Cudkowicz et al 1998].

Persons with the p.Asp90Ala mutation can present with ataxia, which can confuse the diagnosis initially. The p.Asp90Ala mutation is also noteworthy for its ethnic distribution and inheritance. For individuals in northern Sweden and Finland, homozygotes for the p.Asp90Ala mutation have ALS while heterozygotes remain unaffected [Sjalander et al 1995]. Symptomatic heterozygotes have been identified in other populations, although they often have a slowly progressive course [Al-Chalabi et al 1998]. One family was identified as possibly having autosomal recessive ALS with a characteristic phenotype of lower limb onset, slow disease duration, and age of onset between 30 and 45 years. Affected individuals of this family are compound heterozygous for a p.Asp90Ala mutation and a p.Asp96Asn mutation; those family members who are heterozygous for one mutation only did not manifest the disease [Hand et al 2001]. No other families with the p.Asp96Asn mutation have been reported; thus, it cannot be determined if this is a true recessive mutation.

ALS3. In one large pedigree, presentation typical of ALS began in the legs for the majority of individuals; onset was 45 years and duration was five years. No atypical features, such as pain, dementia, sensory loss, or cerebellar degeneration, were observed.

ALS4 (Juvenile-onset motor neuron disease with dominant inheritance and no bulbar involvement. Onset is in adolescence. The duration can be long with some persons living a full life span. ALS4 is associated with slowly progressive distal muscle weakness and atrophy with UMN signs, normal sensation, and absence of bulbar involvement [Rabin et al 1999]. De Jonghe et al (2002) identified three additional families of Belgian, Austrian, and English ancestry. ALS4 is associated with mutations in the *SETX* gene encoding the protein senataxin, which constitutes a DNA/RNA helicase domain with a possible role in RNA processing [Chen et al 2004]. Mutations in *SETX* have also been identified in ataxia and oculomotor apraxia type 2 (AOA2).

ALS6. The clinical presentation is limb onset of disease and bulbar signs with a mean age of onset for four family members of 50.25 years (range 37-66 years) and duration of disease reported in two family members of 36 months and 20 years. In one family of 15 affected individuals, penetrance was 83% by age 70 years. All affected individuals had limb onset with a mean age of onset of 38 years (range 29-51 years) and mean survival of 13 months (range 7-27 months). The other family of eight affected individuals with several obligate heterozygotes had a penetrance of 39% by age 70 years, with four affected individuals having bulbar disease onset and two having suggested FTD/ALS with a mean age of onset of 61 years (range 40-72 years) and mean survival of 35.5 months (range 12-90 months).

One of the families previously reported as linked to 16q12 [Ruddy et al 2003] has recently shown linkage to 9p [Vance et al 2006]; further studies are ongoing to confirm linkage and identify the causative gene in the family.

ALS7. Linkage has been identified in one pedigree with two of fifteen affected sibs with an obligate heterozygote parent, raising the possibility of incomplete penetrance [Sapp et al 2003]. Clinical presentation was not reported.

ALS8. Known as SMAIV, or Finkel type SMA, ALS8 is characterized by primarily LMN findings with UMN findings in some families. ALS8 is caused by mutations in *VAPB*, which encodes a protein that acts during ER-Golgi transport and secretion [Nishimura et al 2004]. The same p.Pro56Ser mutation was identified in one large family and six additional kindreds, all of whom have different courses (ALS8, late-onset SMA, and ALS with rapid progression). Haplotype analysis revealed that the p.Pro56Ser mutation is a founder mutation in individuals of Portuguese/Brazilian and African/Brazilian ancestry, a finding consistent with the Portuguese colonization of Brazil [Nishimura et al 2004].

ALS/frontotemporal dementia (FTD) syndrome. Individuals in families with this syndrome have an FTD syndrome of behavioral change with relatively intact memory associated with signs of motor neuron disease. Genetic heterogeneity exists. The newly described locus on 9p21 is possibly the locus for this disorder.

***BSCL2*-related neurologic disorders.** The spectrum of *BSCL2*-related neurologic disorders includes **Silver syndrome** and **variants of Charcot-Marie-Tooth disease type 2, distal hereditary motor neuropathy type V**, and **spastic paraplegia 17 (SPG 17)**. Features of these disorders include slow disease progression, upper motor neuron involvement (i.e., gait disturbance with pyramidal signs ranging from mild to severe spasticity with hyperreflexia in the lower limbs and variable extensor plantar responses), lower motor neuron involvement (i.e., amyotrophy of the peroneal muscles and small muscles of the hand), abnormal vibration sense, and pes cavus and other foot deformities. Onset of symptoms ranges from the first to the seventh decade.

IBMPFD. Inclusion body myopathy associated with Paget disease of bone and/or frontotemporal dementia (IBMPFD) is characterized by adult-onset proximal and distal muscle

weakness, early-onset Paget disease of bone, and premature frontotemporal dementia. IBMPFD is caused by a gene encoding VCP, which is associated with cellular activities including cell cycle control, membrane fusion, and the ubiquitin-proteosome degradation pathway.

Autosomal Recessive ALS (see Table 2)

Table 2. Molecular Genetics of Autosomal Recessive ALS

% Individuals with Familial ALS	Locus Name	Gene Symbol	Chromosomal Locus	Protein Name	References
Rare	ALS2	*ALS2*	2q33	Alsin	Hentati et al 1994, Yang et al 2001
Rare	ALS5		15q15.1-q21.1		Hentati et al 1998
Rare	SPG20 [1]	*SPG20*	13q12.3	Spartin	Patel et al 2002

1. ALS-related motor neuron disorders with both UMN and LMN involvement

ALS2. Alsin-related disorders (*ALS2*-related disorders) involve retrograde degeneration of the upper motor neurons of the pyramidal tracts, which at onset appears as infantile ascending spastic paralysis (IAHSP), but all reported cases eventually end up as primary lateral sclerosis (JPLS). Other families also have lower motor neuron involvement resulting in a picture of upper motor neuron predominant ALS. *ALS2*-related disorders are characterized by onset during childhood (mean age of onset is 6.5 years), spasticity of facial muscles, uncontrolled laughter, spastic dysarthria, spastic gait, inconstant moderate muscle atrophy, bladder dysfunction, and sensory disturbances; some individuals are bedridden by age 12 to 50 years. *ALS2* makes two transcripts of the protein by alternate splicing of a long form (resulting in juvenile-onset PLS) and a short form (resulting in juvenile-onset ALS) [Yang et al 2001]. Mutations in *ALS2* have not been identified in individuals with adult-onset ALS [Hand et al 2003].

ALS5. Families with ALS5 from Tunisia, South Asia, and Germany have onset between eight and 18 years of age, with both UMN and LMN signs, fasciculations and atrophy of the tongue, and occasionally, mild mental retardation [Hentati et al 1998].

Additional families that are not linked to 2q or 15q exist.

SPG20. Troyer syndrome is characterized by spastic paraparesis with dysarthria, distal amyotrophy, mild developmental delay, and short stature. Most affected children have delay in reaching the early developmental milestones (walking and talking), followed by slow deterioration in both gait and speech. Emotional lability and affective disorders such as inappropriate euphoria and/or crying are common. Mild cerebellar signs are common. The most severely affected individuals have choreoathetosis. It is caused by mutations in *SPG20*, encoding the protein spartin, which may be involved in endosomal trafficking.

X-Linked Dominant ALS

Linkage to the X chromosome has been established in at least one large family with adult-onset FALS in which no male-to-male transmission was evident. Clinically this family had classic UMN and LMN involvement, with UMN signs typically preceding LMN signs. Male family members also had much earlier onset than females, often by age 20 years [Hong et al 1998]. A putative X-ALS gene has been identified and an animal model based on that mutation has impaired behavior and widespread dendritic pathology [Siddique et al, unpublished observation].

Sporadic ALS

About 90% of ALS occurs in individuals with no family history of ALS; such individuals are said to have sporadic ALS (SALS). Note: True sporadic ALS needs to be distinguished from inherited ALS that occurs in simplex cases (i.e., affected individuals who have no family history of the disorder). For example, because of the decreased penetrance of some *SOD1* mutations, an individual with an *SOD1* mutation may sometimes be the only known affected family member (i.e., a simplex case) and thus appear to represent a sporadic case [Jones et al 1995, Orrell et al 1995].

The etiology of sporadic ALS is unknown but is thought to be multifactorial. A combination of oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, inflammation, and apoptosis has repeatedly been proposed [Cleveland & Rothstein 2001], but not validated.

- Mutations in vascular endothelial growth factor (VEGF) have also been proposed as playing a role in modifying ALS [Lambrechts et al 2003]. Although VEGF and related proteins probably have a biological role in ALS, it is unlikely an etiological role [Chen et al 2006].
- Mutations in APOE, in particular the E*2 allele, may protect against the early onset of ALS [Li et al 2004].
- Single nucleotide polymorphisms (SNPs) in the paraoxonase gene cluster (PON) on chromosome 7q have recently been associated with sporadic ALS [Saeed et al 2006]. Serum paraoxonase is associated with high density lipoprotein (HDL) and polymorphisms in PON are associated with increased risk of coronary heart disease. PON enzymes are involved in the metabolism of intrinsic oxidized lipoid products and xenobiotics such as insecticides and nerve gas agents as well as statin drugs.

Evaluation Strategy

Once the diagnosis of ALS has been established in an individual, the following approach can be used to determine the specific subtype of ALS to aid in discussions of prognosis and genetic counseling. Establishing the specific subtype of ALS in a given individual usually involves obtaining family history and performing molecular genetic testing.

Family history. A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or by review of their medical records including the results of molecular genetic testing, neuroimaging studies, and the results of autopsy examinations.

Molecular genetic testing. Molecular genetic testing should be accompanied by formal genetic counseling.

- ***SOD1***testing is appropriate in any individual with ALS who has another affected family member or an incomplete family history, including the early death of a close relative from any cause. Approximately 20% of individuals with FALS have ALS1 with an identified disease-causing mutation in *SOD1*. Interpretation of the significance of an *SOD1* mutation regarding disease severity and progression depends on the specific mutation identified because of wide variability in genotype/phenotype correlations. Failure to detect an *SOD1* mutation does not rule out FALS.

  Up to three percent of individuals with ALS with no family history of ALS have *SOD1* mutations. Since data are limited on penetrance of many mutations, establishing risk for other family members to develop clinical symptoms can be difficult.

- ***ALS2* and *SETX*** testing is appropriate in kindreds with juvenile-onset ALS without bulbar involvement or onset before the age 25.
- ***VAPB*** testing is clinically available and should be pursued in the context of clinical symptoms of primarily spinal muscular atrophy phenotype.
- **Other.** Molecular genetic testing for the other genetic forms of ALS is not clinically available (see Table 3).

Table 3. Molecular Genetic Testing Used in ALS

Phenotype	% of Affected Individuals by Family History		Genetic Mechanism	Test Availability
	Positive	Negative		
Adult-onset LMN-predominant ALS	20%	3%	Mutations in *SOD1*	Clinical Testing
Childhood-onset UMN-predominant ALS	Rare	Rare	Mutations in *ALS2*	Clinical Testing
Adult-onset spinal muscular atrophy	Rare	Rare	Mutations in *VAPB*	Clinical Testing
Adolescent-onset spinal muscular atrophy with pyramidal features	Very rare	Very rare	Mutations in *SETX*	Clinical Testing

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Familial amyotrophic lateral sclerosis can be inherited in an autosomal dominant, autosomal recessive, or X-linked dominant manner. Determination of the mode of inheritance is based exclusively on family history.

Risk to Family Members — Autosomal Dominant ALS

Parents of a proband

- Most individuals diagnosed as having autosomal dominant ALS have an affected parent.
- A proband with adult-onset autosomal dominant ALS may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Parents of a proband with an apparent *de novoSOD1* mutation can be offered *SOD1* molecular genetic testing; however, molecular genetic testing should be performed in the context of formal genetic counseling as it would be considered presymptomatic genetic testing.

Note: Although most individuals diagnosed with autosomal dominant ALS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset or reduced penetrance of the disease in the affected parent.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the proband's parents.
- If one of the proband's parents has a mutant allele, the risk to the sibs of inheriting the mutant allele is 50%.
- If neither parent has a mutant allele, the risk to sibs is low. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with autosomal dominant ALS has a 50% chance of inheriting the mutation.

Risk to Family Members — Autosomal Recessive ALS

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and, therefore, carry a single copy of the disease-causing mutation.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib has a 25% chance of inheriting the homozygous mutation and 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 are asymptomatic.

Offspring of a proband. The offspring of an individual with autosomal recessive ALS are obligate heterozygotes (carriers) for a disease-causing mutation.

Other family members of a proband. The sibs of obligate heterozygotes have a 50% chance of being heterozygotes.

Risk to Family Members — X-Linked Dominant ALS

Parents of a proband

- Most individuals diagnosed with X-linked dominant ALS have an affected parent.
- A woman with X-linked dominant ALS may have inherited the ALS mutation from either her mother or her father.
- A man with X-linked dominant ALS may have inherited the ALS mutation from his mother, but he will not have inherited it from his father.
- A proband with X-linked dominant ALS may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* gene mutations is unknown.

Sibs of a proband

- The risk to the sibs of the proband depends upon the status of the parents.
- If a mother is affected, the risk to all sibs is 50%.
- If the father is affected, all of the daughters and none of the sons will inherit the disease-causing allele.

- If neither parent has the mutation, the risk to the sibs of a proband appears to be low. Germline mosaicism remains a possibility, although it has not been reported.

Offspring of a proband

- Every child of a woman with X-linked dominant ALS has a 50% chance of inheriting the mutation.
- All daughters but no sons of men with X-linked dominant ALS will inherit the mutation.

Risk to Family Members — Empiric Risks

None available.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic adults. Presymptomatic testing for *SOD1* and *VAPB* mutations is controversial because of incomplete penetrance, inability to predict the age of onset, and the lack of preventive measures. Because of the individualized nature of predictive testing, consultation with a genetic counselor and a psychologist to obtain informed consent is recommended. At this time, no established testing protocol (as in, e.g., Huntington disease) exists although establishment of such protocols has been suggested [Fanos et al 2004]. However, to err on the side of caution, testing centers often follow a similar protocol.

Testing of at-risk individuals during childhood. Consensus holds that asymptomatic individuals younger than 18 years of age who are at risk for adult-onset disorders should not have testing. The principal reasons against testing individuals during childhood who do not have symptoms are that it removes their choice, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications [Bloch & Hayden 1990, Harper & Clarke 1990]. See also the National Society of Genetic Counselors statement on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents (pdf; Genetic Testing). In addition, no preventative treatment is available.

Individuals younger than age 18 years who are symptomatic usually benefit from having a specific diagnosis established.

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 for ALS caused by mutations in *SOD1*, *ALS2*, *SETX*, or *VAPB* 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 ten to 12 weeks' gestation. The disease-causing mutation in the 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.

No laboratories offering molecular genetic testing for prenatal diagnosis for ALS caused by mutations in other genes are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Performing prenatal testing for the disease-causing mutation prior to performing genetic testing on the parent (including presymptomatic genetic testing) could reveal the parent's gene status; therefore, genetic counseling is indicated in all considerations of prenatal testing for ALS.

Requests for prenatal testing for adult-onset conditions such as ALS are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Management

Treatment of Manifestations

Treatment is palliative and many individuals benefit from care by a multidisciplinary team including a neurologist, specially trained nurses, pulmonologist, speech therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetic counselor.

Data suggest that individuals under the care of such a team may have a better prognosis [van den Berg et al 2004, Andersen et al 2005]. The factors influencing survival include age, vital capacity, fatigue, body strength, spasticity, household income, and depression [Paillisse et al 2005], most of which can be managed by the appropriate specialist in the multidisciplinary team.

Riluzole is the only currently FDA-approved drug for the treatment of ALS. Its mechanism of action is thought to be glutamate inhibition. Clinical trials have shown marginal slowing of disease progression in some but not all individuals [Bensimon et al 1994, Riviere et al 1998]. Riluzole is associated with elevation of serum alanine aminotransferase levels in 10% to 15% of treated individuals and may rarely cause bone marrow depression [Bensimon & Doble 2004].

Oral secretions in individuals with bulbar symptoms can be reduced with tricylic antidepressants and anticholinergic agents, thus reducing the need for suctioning.

Pseudobulbar affect can be managed with antidepressants, such as Neurodex (dextromethophan and quinidine).

Swallowing difficulties can be alleviated by thickening liquids and pureeing solid food, and eventually use of a gastrostomy tube to help maintain caloric intake and hydration. Nutritional management, a prognostic factor for survival, has become a focus in the clinical setting.

Medications such as baclofen and benzodiazepines can help relieve spasticity and muscle cramps; however, weakness and lethargy are common side effects. Individualized, moderate

intensity, endurance type exercises for the trunk and limbs may help to reduce spasticity [Ashworth et al 2004].

Low-tech (e.g., alphabet board) and high-tech (i.e., computer-assisted) devices can aid speech and communication. The recent development of the eye movement-controlled on-screen keyboard may enable communication for individuals without any remaining limb function.

Assistive devices, such as walkers or wheelchairs, can aid mobility, and others, such as bathroom installments, hospital bed, and hoyer lift, can aid in activities of daily living at home.

Ventilatory assistance may include use of bilevel positive airway pressure (BIPAP), which has played an increasing role in preserving and prolonging quality of life in persons with ALS. In 1999, the American Academy of Neurology published norms recommending the initiation of non-invasive ventilation (NIV) in individuals with a theoretical forced vital capacity (FVC) less than 50% of predicted [Miller et al 1999]. Recent studies show that mean survival significantly increases when NIV is initiated prior to the onset of bulbar symptoms [Farrero et al 2005]. Therefore, evaluation by a pulmonologist should be undertaken prior to reduction of the forced vital capacity below 50%.

Although tracheostomy and ventilatory support can extend life span, affected individuals often decline these interventions [Albert et al 1999].

The tremendous psychological and social impact of ALS on both affected individuals and caregivers needs to be continually addressed [Goldstein et al 1998]. Hospice care, typically instituted once FVC is less than 30%, contributes to comfort of the individual in the terminal stages.

Therapies Under Investigation

Xaliproden slowed the rate of deterioration in FVC by 43% in individuals with ALS during Phase II safety and efficacy trials performed in France, but did not improve functional or manual muscle testing scores [Lacomblez et al 2004]. Further investigations are needed.

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

Other

Individuals with ALS commonly supplement their diets with vitamin E, vitamin C, B vitamins, selenium, zinc, coenzyme Q10, and herbal preparations such as ginseng, gingko biloba, and Maharishi Amrit Kalesh [Cameron & Rosenfeld 2002]. In a Cochrane Review, Orrell et al (2006) summarized and evaluated 21 clinical trials of antioxidant therapies in various combinations including vitamin E, high-dose coenzyme Q10, vitamin C, selenium, beta-carotene, N-acetylcysteine, L-methionine, and selegiline. In the majority of these studies, the sample size was not adequate for statistical evaluation. Although the antioxidants were well tolerated in many of the trials, significant differences in longevity, muscle strength, or functional rating scales over time were not identified.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

Amyotrophic Lateral Sclerosis Association (ALSA)
27001 Agoura Road Suite 150
Calabasas Hills CA 91301-5104
Phone: 800-782-4747 (patient hotline); 818-880-9007; 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 Suite 300
Toronto M2J 1S5
Canada
Phone: 800-267-4ALS (800-267-4257); 416-497-2267
Fax: 416-497-1256
Email: SI@als.ca
www.als.ca

Les Turner ALS Foundation
5550 W. Touhy Avenue Suite 302
Skokie IL 60076-3254
Phone: 888-ALS-1107 (888-257-1107); 847-679-3311
Fax: 847-679-9109
Email: info@lesturnerals.org
www.lesturnerals.org/

National Library of Medicine Genetics Home Reference
Amyotrophic lateral sclerosis

NCBI Genes and Disease
Amyotrophic lateral sclerosis

Muscular Dystrophy Association (MDA)
3300 East Sunrise Drive
Tucson AZ 85718-3208
Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

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Chapter Notes

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- 21 November 2007 (cd) Revision: prenatal diagnosis for *SETX* mutations available clinically
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