Published in final edited form as:
Neurol Clin. 2013 November ; 31(4): . doi:10.1016/j.ncl.2013.05.003.

Clinical Neurogenetics: Amyotrophic Lateral Sclerosis

Matthew B. Harms[1,2] and **Robert H. Baloh**[3,4]

[1]Department of Neurology, Neuromuscular Division, Washington University School of Medicine, St. Louis, MO 63110, USA

[2]Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO 63110, USA

[3]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA 90048

[4]Regenerative Medicine Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048

Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, about which our understanding is expanding rapidly as its genetic causes are uncovered. The pace of new gene discovery over the last 5 years has accelerated, providing new insights into the pathogenesis of disease and highlighting biological pathways for target for therapeutic development. This article reviews our current understanding of the heritability of ALS, provides an overview of each of the major ALS genes, highlighting their phenotypic characteristics and frequencies as a guide for clinicians evaluating patients with ALS.

INTRODUCTION

Definition

Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease or motor neuron disease, is fatal neurodegenerative disease characterized by the progressive loss of cortical, brainstem, and spinal cord motor neurons.

Symptoms and Clinical Course

The classic clinical symptoms of ALS arise from the progressive loss of both upper motor neurons (UMN) located in the cerebral cortex and lower motor neurons (LMN) located in brainstem nuclei or anterior horn of the spinal cord. However, ALS is increasingly recognized as a multisystem neurodegenerative disease, in which motor neurons are particularly, but not exclusively, involved[1–3]. As a result, degeneration of non-motor system neurons occurs and results in clinically recognizable symptoms.

- LMN degeneration produces:
  - Muscle cramping and fasciculations, even before weakness occurs
  - Atrophy of affected muscles

Correspondence to: Matthew B. Harms, MD, 660 S. Euclid Avenue, St. Louis, MO 63110 (harmsm@neuro.wustl.edu); or Robert H. Baloh, MD, PhD, 8730 Alden Drive, Los Angeles, CA 90048 (robert.baloh@csmc.edu).

  - Weakness
- UMN degeneration produces:
  - Slowed movement and weakness in a pyramidal distribution
  - Uncoordinated movements, particularly of fine manipulation
  - Spastic tone
  - Increased deep tendon reflexes, sometimes with spread or clonus
  - Lost regulation of laughing and/or crying (pseudo-bulbar affect)
- Non-motor system degeneration can produce:
  - Executive dysfunction in a majority of patients (loss of frontotemporal neurons)[32]
  - Frontotemporal dementia in ~5% (loss of frontotemporal neurons)[4, 5]
  - Parkinsonism (basal ganglia)[6, 7]
  - Sensory loss (doral root ganglia)[8, 9]

ALS is commonly diagnosed according to the revised El Escorial Criteria[10, 11]. These criteria require:

- Evidence of lower motor neuron (LMN) degeneration by clinical examination, neurophysiologic testing, or pathological examination in ≥1 of 4 body regions (bulbar, cervical, thoracic, lumbar)
- Evidence of upper motor neuron (UMN) degeneration by clinical examination
- Progressive spread of signs within a body region or to additional body regions
- Exclusion of causes other than ALS by appropriate testing (e.g. laboratory, imaging, electrodiagnostic)

These criteria were initially developed for research purposes but are routinely applied in many neuromuscular clinics to specify the certainty of an ALS diagnosis according to definite, probable, and possible categories (Table 1).

The clinical phenotype of a given ALS patient depends on the location, degree, and proportion of LMN, UMN, and non-motor involvement. At one end of the spectrum are patients with progressive muscular atrophy (PMA) where only LMN involvement is clinically apparent. Primary lateral sclerosis (PLS) occupies the other end, with UMN involvement as its defining feature. Current evidence suggests that the majority of PMA and PLS cases eventually progress to meet criteria for ALS and are therefore diseases on the ALS spectrum[12–15]. Furthermore, sequencing studies highlight identical genetic causes[16]. Many lines of evidence also support ALS and frontotemporal dementia (FTD) as two ends of a clinical spectrum, including clinical observations, co-occurrence in patients, shared neuropathologic findings, and genetic causes in common (reviewed in [17, 18]).

ALS phenotypes are frequently classified by the site of symptom onset. Two-thirds of patients have onset in the limbs (“spinal onset”), with an approximately equal distribution between upper and lower extremities[19–21]. The remaining one-third of patients first experience difficulties with speech or swallowing (“bulbar onset”). Regardless of the site of onset or initial phenotype, the relentless loss of motor system neurons leads to progressive paralysis and eventually to terminal respiratory failure. The rate of disease progression varies widely, but for a given patient appears fairly linear, possibly with faster rates of

decline in early and late disease[22]. Median survival estimates center on 32 months[23] from symptom onset, but varies from 23–48 months[24–28]. However, 20% of patients survive 5 years and 10% are still living after a decade[23]. Across multiple studies, bulbar onset ALS is consistently found to be more common in women, shows a later age of onset, and is associated with a poorer prognosis[29–32]. An earlier age of onset, a family history of ALS, and presentation with primary lateral sclerosis are consistent predictors of longer survival [19, 21, 32]. Studies suggest that improvements in supportive care, including earlier use of non-invasive ventilation are improving survival trends[28, 33]. Riluzole is the only medication approved for the treatment of ALS and improves survival by 2–3 months[34].

Nature of Disease

The incidence of ALS is generally consistent across diverse populations at 1–3/100,000[35–42], producing a lifetime risk of 1 in 300–1000[43, 44]. ALS is more common in men, typically by a ratio of 1.3[19, 29, 45], but this gender gap may be disappearing due to a rising incidence of ALS among women[44, 46].

Beginning with the earliest descriptions of the disease, hereditary forms of ALS have been apparent[47] and prompted categorization into familial and sporadic forms (FALS and SALS respectively). The vast majority of FALS cases show autosomal dominant inheritance, with X-linked and recessive patterns being rare. The prevalence of familial ALS (FALS) is widely cited to be 10%, but this number depends greatly on the population sampled and the definition of FALS utilized (for which is there is currently no clear consensus[48]). For example, regional clinic-based series report FALS rates as high as 23%[49, 50] while prospective population-based analyses suggest the number may be closer to 5% with modest geographical variability[51]. It has been proposed that the definition of FALS should take into consideration a family history of other neurodegenerative diseases, including FTD[52] (Table 2).

Clinical Findings

Physical Examination—Physical examination findings in early ALS are highly variable, and in a given patient depend on the site of symptom onset, the relative contributions of upper and lower motor neuron degeneration, and the degree of extra-motor involvement. No examination findings reliably distinguish FALS from SALS, or definitively differentiate between specific genetic causes.

Other Diagnostic Modalities—Nerve conduction studies and electromyography (EMG/NCS) play an important role in identifying the degree and extent of lower motor neuron loss in ALS. Furthermore, they are utilized to exclude important mimics of ALS, including radiculopathy, polyneuropathies, and multifocal motor neuropathy. MRI and analysis of cerebrospinal fluid are also frequently utilized to ruleout infectious polyradiculitis, carcinomatosis, lymphomatosis, and other mimics of ALS.

Genetic Basis of Disease

Rapid advances in DNA sequencing technologies have accelerated the pace of gene discovery and revealed an impressive genetic heterogeneity in ALS. Mutations in more than 22 genes have now been described in patients with ALS or ALS-like phenotypes, with more than half of these representing clear moderate or high-penetrance causative genes (Table 3). Before reviewing what is known about the most important of these genes, several themes have been highlighted by these discoveries:

1. **Genotype-phenotype correlations are imprecise in most cases.**

As is often the case with adult-onset, autosomal dominant disease, the clinical manifestations of each gene and each specific mutation show broad clinical heterogeneity. Even within a given pedigree, the age of onset can span decades, the ALS phenotype can range from pure LMN syndrome to pure FTD, and the course of the disease can range from fast progression to prolonged survival. There are some identifiable broad trends in phenotypes (e.g., *SOD1* mutations tend to have lower extremity onset with predominantly LMN manifestations, *TARDBP* mutations are more commonly upper extremity onset, *C9ORF72* expansions have an increased rate of bulbar onset and of accompanying FTD), but for each gene, many cases disprove the rules. As a result, it is usually difficult to predict which gene might be mutated in a given pedigree or patient.

2. **Mutations in known ALS genes also explain a minority of patients with SALS.**

   This fact is not surprising given the fact that familial and sporadic ALS are virtually indistinguishable in the clinic and under the microscope, showing similar ranges of onset, survival, phenotype, and neuropathological features. Mathematical models considering current demographic trends (e.g. increasingly smaller family sizes), predict that moderate and even high-penetrance mutations would appear sporadic at approximately the same rate observed in empirical cohorts[53].

3. **In a surprising number of cases, more than one ALS-associated mutation may be found.**

   As the simultaneous sequencing of panels of ALS genes has increased with declining costs of sequencing, patients with mutations in more than one gene are being reported. Most commonly, the *C9ORF72* expansion is found alongside a second mutation, but co-occurrence has also been noted for other combinations of genes, including *FUS* with *ANG*[54], *UBQLN2* with *TARDBP* or *OPTN*[55]. These cases are possible examples of “oligogenic” inheritance, where-in clinical manifestations of disease are influenced by the presence of both mutations. At this point however, the number of “two-hit” cases is small and it is unclear whether second mutations influence penetrance, disease phenotype, or progression.

C9ORF72

In 2006, FALS pedigrees were first linked to chromosome 9p21[56], with a notable cooccurrence of ALS and FTD. This pedigree and additional 9p21-linked ALS/FTD families were recently shown to carry a massive expansion of a hexanucleotide repeat in the first intron of *C9ORF72*[57, 58]. Whereas normal individuals carry 2–30 of the GGGGCC repeat units, pathological expansions are at least 700–2400 repeat units in length, show a tremendous degree of somatic variability, and appear to be larger in neuronal tissue than elsewhere[59]. Due to a Northern European founder mutation, the prevalence *of* C9ORF72 expansions is highest in white populations where it explains 37% of FALS, 25% of familial FTD, and ˜6% of sporadic cases of ALS or FTD [60]. However, the mutation is found worldwide[61].

The function of *C9ORF72* is currently unknown, but recent studies suggest it may function as a guanine exchange factor (GEF) for Rab GTPases[62, 63]. How a non-coding expansion in the gene causes neurodegeneration is not currently known, but emerging evidence supports:

- Loss-of-function: repeat expansions reduce allele-specific expression by as much as 50%[57, 64].
- Gain-of-function:

- Repeat-containing RNA transcripts[57] form intranuclear foci, believed to sequester required RNA binding proteins and lead to disrupted gene expression and dysregulated alternative splicing, as is the case for myotonic dystrophy (reviewed in[65]).
- Repeat-associated non-ATG dependent translation (RANT) of the GGGGCC repeat itself produces repetitive dipeptides that aggregate in the cytoplasm of affected cells[66, 67].

The *C9ORF72* repeat expansion most commonly presents with ALS, ALS-FTD, or pure FTD, and is associated with an increased incidence of bulbar symptom onset, an earlier age of onset, and statistically shorter survival. The expansion has also been found in patients with other neurodegenerative syndromes, including Alzheimer's disease, Parkinson's disease, corticobasal degeneration, and ataxia[68–71]

SOD1

In 1993, *SOD1,* encoding copper/zinc superoxide dismutase, was the first causative gene identified for ALS[72]. In the 20 years since, more than 160 mutations have been reported, involving almost every amino acid of the protein (http://alsod.iop.kcl.ac.uk/). *SOD1* mutations account for 15–20% of FALS pedigrees[73, 74] and until the discovery of *C9ORF72* was the most commonly identified gene in ALS. This likely remains true in many non-white populations, where *C9ORF72* is much less common.

Despite the fact that *SOD1* is the best studied of all ALS genes, our understanding of its pathogenic mechanism is incomplete. *SOD1* is a ubiquitously expressed cytosolic protein known to neutralize superoxides. Interestingly, several clearly pathogenic mutations have no effect on the dismutase activity of SOD1 and reduced enzyme activity shows no correlation with disease severity, suggesting that a gain-of-function mechanism most likely explains pathogenesis[75]. Misfolding of SOD1 is likely to be important, with downstream disruption of mitochondrial function, oxidative stress, endosomal trafficking, and excitotoxicity (reviewed in[76]).

SOD1-associated ALS is clinically heterogeneous but shows several phenotypic trends warranting mention. First, cognitive impairment is infrequent and FTD is rare[77]. Second, in most patients, UMN findings are minimal or absent and the clinical picture is dominated by LMN degeneration[78]. Finally, because large numbers of patients with individual mutations have been studied, some genotypephenotype correlations can be made: p.A5V (also called A4V) is associated with rapidly progressive disease, while other mutations (including p.G38R and p.D11Y) are uniformly slow [79, 80]. A recessive form found in Scandinavia is due to homozygous p.D91A mutations and causes a characteristic ascending paralysis due to LMN degeneration[81].

TARDBP

One consistent pathologic finding in ALS and FTD cases is the presence of heavily ubiquitinated neuronal cytoplasmic inclusions, which in 2006 were found to contain TDP-43, encoded by the *TARDBP* gene[82]. Mutations in *TARDBP* were soon found to cause ALS[83–85] and later, FTD[86]. *TARDBP* causes 3–5% of FALS and <1% of SALS, although founder mutations make it more common in some areas[49].

TDP-43 is a DNA/RNA binding protein with broad roles in RNA metabolism[87, 88], including microRNA biogenesis[89]. Almost all pathogenic mutations affect the C-terminal glycine-rich domain, the function of which is still being uncovered. Mutations in this domain result in the translocation of TDP-43 from the nucleus to the cytoplasm, where it

forms the hallmark aggregates. Whether it is nuclear depletion of TDP-43, cytoplasmic aggregation, or both that causes neurodegeneration is an area of active investigation using an expanding list of cellular and animal models.

Patients with *TARDBP* mutations have an earlier age of onset and longer disease duration[90], but otherwise share the broad range of presentations with sporadic ALS. Upper extremity onset is the most common presentation, which may help differentiate from patients with *SOD1* mutations[90]. Some patients have extra-pyramidal involvement and rarely present with pure parkinsonism [91, 92]. Cooccurrence of FTD with ALS is common, but pure FTD has also been reported[86].

FUS

Not long after the discovery of TARDBP, linkage of ALS families to chromosome 16 revealed mutations in another RNA binding protein called FUS[93, 94]. Broader screening of this gene in FALS cohorts has shown a frequency of 1–8% of Caucasian pedigrees[95–97], but a much higher frequency (10–13%) in Asian populations[98–100]. A similar trend is recognized in SALS, where the FUS mutation rate is 0–0.74% [95, 101, 102] among Caucasians but approaches 2% in Asian studies[100, 103]. The vast majority of families show autosomal dominant transmission, but recessive inheritance[93] and *de novo* cases with juvenile onset and rapid progression are also reported[104, 105].

FUS is a member of the "FET" family of proteins along with EWSR1 and TAF15, which have also been implicated in ALS[106, 107]. As with *TARDBP*, disease associated mutations cluster in the C-terminal domain and cause mislocalization of FUS from the nucleus into the cytoplasm, where it is found in cytoplasmic aggregates[93, 94]. Interestingly, the degree of impaired nuclear localization correlates with the age of onset for a given mutation [108]. *FUS* mutations, with their cytoplasmic redistribution are hypothesized to cause neurodegeneration by a combination of mechanisms focused on i) loss of its normal functions in the nucleus (microRNA biosynthesis, gene expression regulation, alternative splicing) and ii) a toxic gain-of-function in the cytoplasm (stress-granules, aggregation).

FUS mutations are associated with predominantly lower motor neuron symptoms[109] and most show incomplete penetrance[110]. In comparison to other causes of FALS (including *SOD1*), *FUS* mutation carriers show earlier onset and shorter survival[54, 111]. Several specific mutations, especially p.P525L, typically arise *de novo* and have an early enough onset to be classified as juvenile ALS[112]. Truncation mutations resulting in deletion of the C-terminal nuclear localization domain also show more aggressive disease[97]. A broader set of phenotypes is also rarely associated with FUS mutations, including behavioral-variant FTD[113]. Mutations in FUS have also been reported in familial essential tremor, but screening of other cohorts has failed to find additional families [114].

UBQLN2

Candidate gene sequencing in a large family with X-linked inheritance of ALS-FTD led to the recent identification of *UBQLN2* as a cause of ALS[115]. *UBQLN2* mutations are found in up to 2% of families without evidence of male-to-male transmission, but have proven rarer in other large FALS cohorts[55, 116–118]. Interestingly, the earliest reported mutations all disrupt proline residues in a unique, but highly conserved, PXX domain[115]. Subsequent studies have uncovered a few additional families with PXX domain mutations and two Australian pedigrees have been reported with a pathogenic mutation adjacent to this domain[119]. Screening in patients with SALS have uncovered additional novel variants with a frequency of ~1%[120], but most fall outside the PXX domain and their pathogenicity is

currently uncertain[116, 121]. Phenotypes associated with *UBQLN2* mutations include ALS, ALS with FTD, and juvenile onset ALS[115].

Ubiquilin 2 is one of four members of the ubiquitin-like family, with roles in delivering ubiquitinated proteins to the proteasome for degradation. *UBQLN2* alone has the unique PXX domain in which most mutations have been found, and it is hypothesized that this domain and its proline residues are important for the specificity of protein-protein interactions[115]. UBQLN2 localizes to the same neuronal cytoplasmic inclusions that stain for TDP-43, FUS, and OPTN, not just in the spinal cords of patients with *UBQLN2* mutations, but in all ALS patients studied[115, 122].

PFN1

Exome sequencing recently identified *PFN1* mutations in ALS[123]. Although this gene explained 1–2% of families in the initial study, its frequency is likely much lower: only one additional family[124] has been found despite screening in large ALS or FTD cohorts from around the world [121, 125–127]. Furthermore, ~1 in 1000 SALS patients screened has a p.E117G mutation[123, 128], but the pathogenicity status of this variant is currently unclear- it is found in control datasets at half the frequency as in SALS but by functional studies appears to be a milder mutation[123].

Profilin 1 is essential for the polymerization of monomeric G-actin into filamentous actin with roles in axonal integrity and axonal transport. These roles may be important to motor neuron degeneration as other cytoskeletal pathway genes are also implicated in ALS, including *DCTN1*, *NEFH*, *spastin* and *peripherin*. All ALS-associated mutations described to date are missense variants affecting amino acids in close proximity to actin binding residues. Not surprisingly, all but the milder p.E117G mutation show decreased actin binding, and when overexpressed, inhibit neurite outgrowth, reduce the size of axonal growth cones and alter growth cone morphology[123]. Furthermore, the expression of mutated PFN1 in N2A cells and primary neuronal culture results in ubiquitinated cytosolic aggregates with TDP-43 co-localization, similar to those identified in patients with SALS[123].

Fewer than 30 ALS patients with *PFN1* mutations been reported to date. Strikingly, all have presented with limb onset and none have had significant cognitive impairment or FTD [123, 124], hinting at a consistent phenotype for *PFN1* mutations that may parallel *SOD1*-associated ALS.

ANG

Since angiogenin (*ANG*) was first examined as a candidate gene for ALS, numerous mutations have been reported in both familial and sporadic disease. However, many reported variants lack segregation evidence and are now recognized as rare variants in the population (e.g. 1000 Genomes Project or NHLBI's Exome Variant Server). These *ANG* variants might function as low penetrance mutations, increasing the risk of developing ALS[129]. Recent work demonstrates ALS-associated *ANG* mutations impair the formation of stress granules in neurons[130], which is interesting in light of the recruitment of TDP-43 and FUS to stress granules. Clinical and neuropathologic features of *ANG* associated ALS are typical of ALS in general, without discriminating features[131].

OPTN

Study of Japanese ALS patients identified mutations in *OPTN* as a rare cause of ALS, with both recessive and dominant acting mutations[132]. Subsequent studies have revealed a few additional families and rare mutations in SALS[133–135]. Optineurin is found in TDP-43

positive neuronal aggregates in mutation carriers[132], and can be seen in neuronal aggregates in non-*OPTN* ALS[132]. *OPTN* associated ALS is heterogeneous in its presentation based on the limited number of patients reported to date, and no clear phenotype has yet been identified.

VCP

Mutations in valosin-containing protein (*VCP*) were first shown to cause inclusion body myopathy with Paget's disease and frontotemporal dementia (IBMPFD)[136]. Recently however, it has been recognized that rarely, an ALS phenotype can also be seen[137–141]. A personal or family history of FTD, myopathy, Paget's disease, or an elevated serum alkaline phosphatase (a biomarker for the presence of Paget's) may serve as clues to this genetic cause.

SETX

Mutations in senataxin (*SETX*), a DNA/RNA helicase, were first associated with a juvenile-onset, slowly progressive form of ALS (ALS4)[142]. Screening in more typical ALS patients has uncovered a handful of additional novel or rare variants in SALS, but the pathogenicity of these variants remains unclear [143, 144].

VAPB

A founder mutation in *VAPB* (p.P56S) was first identified in Brazilian families with a spectrum of motor neuron degenerative phenotypes ranging from late onset spinal muscular atrophy to rapidly progressive ALS[145]. Although a large number of FALS and SALS cases have been screened for this gene, only a handful of additional rare or novel variants have been uncovered but with unclear pathogenicity [146–149].

Other Genes

Mutations in additional genes have also been found in patients with ALS, including *FIG4*[150], *DAO*[151], *hnRNPA2B1*[152], *hnRNPA1*[152], *SQSTM1/p62*[153–156], and *DCTN1*[157, 158].

Genomics/Risk Variants

With only 5–10% of sporadic ALS cases harboring disease associated mutations in known ALS genes[159], the remainder of SALS is presumed to be a complex disease influenced by both genetic and environmental exposures. Efforts to identify genetic risk factors have largely focused on genome-wide and candidate gene association studies, with mixed success.

- ***CYP27A1***[160]: Using gene expression and genotyping data from SALS patients, SNPs impacting the expression of *CYP27A1* were recently identified as small effect risk factor for ALS. Validation studies have yet to be reported.
- **Ataxin-2 intermediate length repeats**: Full pathogenic expansions in the CAG repeat (>34 repeats) of *ATXN2* cause spinocerebellar ataxia type 2, a disorder sometimes accompanied by motor neuron degeneration. Investigations of CAG repeat length in SALS identified intermediate-sized repeats (27–33) as a risk factor[161]. Additional studies across multiple populations have confirmed this association [162–169], though the strength of association may be lower in some populations[170]. The link between intermediate repeats in ATXN2 and ALS appears to be due to an interaction with FUS[171] and TDP- 43[172].

- ***UNC13A***: First identified by genome wide association study (GWAS) in 2009[173], variation near *UNC13A* has been replicated as a risk for developing SALS[174], and the minor allele at SNP rs12608932 shows a significant association with reduced survival in patients[174, 175]. UNC13A is a presynaptic protein involved in regulating neurotransmitter release and it has been hypothesized that the increased risk could be due to glutamate dysregulation and resulting excitotoxicity [173].
- ***DPP6:*** DPP6 is a component of type A neuronal transmembrane potassium channels and was first associated with SALS in a GWAS of Irish patients[176], and subsequently validated in other European populations [177, 178]. However, since then, efforts to replicate the association in other populations have failed, leaving the status of this risk factor uncertain[179–183].
- ***ELP3:*** A single study identified risk for ALS in association with alleles of a RNA polymerase component, Elongation protein 3[184]. Although mutations in ELP3 cause neurodegeneration in a drosophila model and increase interest as an ALS candidate gene, other GWA studies have not identified this association.

Evaluation and Management

Strategies for Diagnosis

Obtaining a genetic diagnosis in ALS is challenging due to the overlapping phenotypes and genetic heterogeneity. Given the complicated implications of a genetic diagnosis, the decision to undertake testing warrants careful consideration by patients and their families. Referral to a knowledgeable genetic counselor may help patients make informed decisions in this regard. Five years ago, when causative mutations were identified in only 20% of familial cases, the utility of genetic testing was unclear. Now however, a causative mutation is found in ~2/3 of pedigrees[59], making testing more informative to patients and their at-risk relatives. Typically, the *C9ORF72* repeat expansion is investigated first, since this is the most common mutation in Caucasian populations and cannot be detected using standard sequencing methods. If no expansion is present, direct sequencing of other common genes is usually pursued, either sequentially (typically starting with *SOD1* followed by *TARDBP* and *FUS*) or as a panel. As sequencing costs fall, next-generation sequencing methods are also becoming a cost-effective option. Whole-exome sequencing will screen for mutation in all known ALS genes, with the added benefit that data can be re-analyzed in the future as new genes are discovered. Historically, the yield of genetic testing in sporadic disease was quite low. Now however, the realization 6–10% of apparently sporadic ALS patients carry *C9ORF72* expansions is challenging this belief. Testing for the *C9ORF72* expansion should be considered in SALS, especially if the patient or a close relative has dementia. Other genes are sufficiently rare that further testing is usually of limited utility.

Current Management and Therapeutic Options

While riluzole is the only FDA approved medication for ALS, there are numerous supportive therapies which likely improve quality of life and survival. These include noninvasive positive pressure ventilation[185, 186] and nutritional support via placement of a gastric tube[187]. Most importantly, care in a multidisciplinary clinic setting has been shown to significantly improve prognosis[188], and clinicians should strive to refer their patients to multidisciplinary ALS clinics if available.

Summary

The last 5 years have led to a staggering expansion of our understanding of the genetics of ALS. With these insights we have learned of several key molecular pathways on which to focus basic science research, and therapeutic efforts. The most notable include alterations in

RNA metabolism and protein homeostasis. There is no doubt that the prospects for developing meaningful interventions for ALS patients have never been better, providing hope for ALS patients and their caregivers.

Acknowledgments

This work was supported by National Institutes of Health (NIH) Grants NS055980 and NS069669 (R.H.B), and NS075094 (M.B.H.). R.H.B. holds a Career Award for Medical Scientists from the Burroughs Wellcome Fund.

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KEY POINTS

1. ALS is increasingly genetically heterogeneous as studies have implicated more than 20 genes, at least half of which are definitively causative and represent moderate to high-penetrance genes.
2. Mutations in ALS genes are increasingly recognized in patients with no family history, emphasizing the incomplete ascertainment of familial links as well as the importance of genetic causes in even apparently sporadic cases.
3. With a few notable exceptions, correlations between the mutated gene and the ALS phenotype are imprecise. Thus sequencing approaches targeting the increasing numbers of ALS genes are required, including next-generation based gene panels or whole-exome sequencing.

Table 1

Revised El Escorial Criteria for the classification of ALS diagnostic certainty:

Category	
Definite	• UMN and LMN signs in bulbar region and ≥2 other spinal regions -or- • UMN and LMN signs in 3 spinal regions with progression over 12 months
Probable	• UMN and LMN signs in ≥ 2 regions, with UMN signs above a region with LMN signs *AND* progression over 12 months after diagnosis
Probable, laboratory supported	• UMN and LMN signs in only 1 region, or UMN signs in only 1 region *AND* EMG evidence for LMN degeneration is present in ≥2 regions without another cause.
Possible	• UMN or LMN signs in only 1 region (i.e., progressive bulbar palsy) • UMN signs in ≥2 regions (i.e., primary lateral sclerosis)

Table 2

Proposed Classification of Familial ALS[52]

Category	Criteria
Definite	• ≥3 affected individuals -or- • 2 affected individuals with a segregating of genetic mutation
Probable	• ≥1 affected first or second degree relative(s)
Possible	• An affected relative is more distant than second degree -or- • A “sporadic” patient is found to carry a known genetic mutation -or- • A first degree relative has/had frontotemporal dementia, but not ALS

Table 3

Genetic causes of amyotrophic lateral sclerosis.

Gene	Frequency	Inheritance	Main Phenotype(s)	Other Features
C9ORF72	30–50% of FALS; as high as 10% of SALS	AD	ALS-FTD = ALS only = FTD only	Parkinsonism, psychosis
SOD1	10–20% of FALS; as high as 3% of SALS	AD (rare AR or *de novo*)	ALS; FTD is rare	Often LMN predominant; highly variable
TARDBP	0–62% of FALS; as high as 2% of SALS	AD (rare AR)	ALS; ALS-FTD	Parkinsonism
FUS	1–13% of FALS; as high as 2% of SALS	AD (rare AR and *de novo*)	ALS fFTD	Juvenile ALS; mutations reported in essential tremor
UBQLN2	0–2.6% FALS; rare SALS cases reported	X-linked dominant	ALS-FTD; pure FTD in single patient thus far	Reduced penetrance in females; seen in patients with potential second mutations
ANG	Most common in Irish/Scottish populations	AD	ALS; rare FTD	Rare variants increased in Parkinson's
OPTN	0–4% FALS; rare SALS cases reported	AD, AR	ALS-FTD	Mutations also cause POAG
FIG4	2.8% FALS; 0–1.6% SALS	AD	ALS, UMN predominant	Only 1 additional study reports sequencing FIG4, with 0/80 gene negative SALS
PFN1[123]	0–2.6% FALS; single SALS report	AD	ALS	Only limb onset described thus far
VCP	0–1% FALS; reported in SALS	AD	ALS; ALS-FTD	Mutations also cause IBMPFD
SETX	Rare	AD	Juvenile ALS; dHMN	Recessive mutations cause AOA2
VAPB	Rare in FALS; Novel or rare variants found; segregation not shown	AD	Late-onset SMA; ALS	P56S mutation with best evidence found in Brazilian kindreds
hnRNPA2B1	Single family	AD	ALS IBM-PFD like	
hnRNPA1	Two families; 1 SALS	AD	ALS IBM-PFD like	
DAO	Single FALS pedigree	AD	ALS	
TAF15	Novel or rare variants found in SALS	AD	ALS	N/A
EWSR1	Novel or rare variants found in SALS	AD	ALS	N/A
SQSTM1	Novel or rare variants found; segregation not shown	AD	ALS	Mutations also cause Paget's disease
CHMP2B	Novel or rare variants found; segregation not shown			
NEFH	Novel or rare variants found: segregation not shown	AD	ALS	
DCTN1	Novel or rare variants found; segregation not shown	AD	LMN disease, dHMN	Mutations also cause Perry Syndrome
PRPH	Novel or rare variants found; segregation not shown	AD		
SPG11	Rare	AR	Juvenile ALS; HSP	
ALS2	Rare	AR	Juvenile ALS; juvenile PLS; infantile HSP	

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Gene	Frequency	Inheritance	Main Phenotype(s)	Other Features
SIGMAR1	1 consanguineous family reported	AR	Juvenile ALS	FALS cases later found to carry the C9ORF72 hexanucleotide expansion
ERLIN2	1 consanguineous family reported	AR	Juvenile PLS; HSP	

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; LMN – lower motor neuron; UMN – upper motor neuron; FALS – familial ALS; SALS – sporadic ALS; FTD – frontotemporal dementia; N/A – not applicable; IBMPFD – inclusion body myopathy with Paget's disease and frontotemporal dementia; POAG – primary open-angle glaucoma; AOA2 – ataxia with oculomotor apraxia type 2; dHMN – distal hereditary motor neuropathy; SMA – spinal muscular atrophy; HSP – hereditary spastic paraparesis; PLS – primary lateral sclerosis;