



REVIEW

What causes amyotrophic lateral sclerosis? [version 1; referees: 3 approved]

Sarah Martin , Ahmad Al Khleifat, Ammar Al-Chalabi

Maurice Wohl Clinical Neuroscience Institute, King's College, London, UK

v1

First published: 28 Mar 2017, 6(F1000 Faculty Rev):371 (doi: 10.12688/f1000research.10476.1)

Latest published: 28 Mar 2017, **6**(F1000 Faculty Rev):371 (doi: 10.12688/f1000research.10476.1)

Abstract

Amyotrophic lateral sclerosis is a neurodegenerative disease predominantly affecting upper and lower motor neurons, resulting in progressive paralysis and death from respiratory failure within 2 to 3 years. The peak age of onset is 55 to 70 years, with a male predominance. The causes of amyotrophic lateral sclerosis are only partly known, but they include some environmental risk factors as well as several genes that have been identified as harbouring disease-associated variation. Here we review the nature, epidemiology, genetic associations, and environmental exposures associated with amyotrophic lateral sclerosis.

Keywords

amyotrophic lateral sclerosis, neurodegenerative disease, motor neuron disease



F1000 Faculty Reviews are commissioned from members of the prestigious F1000
Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 Robert P. Bowser, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, USA
- 2 Richard W Orrell, University College London Institute of Neurology, UK
- Mamede de Carvalho, Institute of Physiology, Faculty of Medicine, University of Lisbon, Portugal Department of Neurosciences, Hospital de Santa Maria, Portugal

Discuss this article

Comments (0)



Corresponding author: Sarah Martin (sarah.martin@kcl.ac.uk)

Competing interests: The authors declare that they have no competing interests.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2017 Martin S *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Martin S, Al Khleifat A and Al-Chalabi A. What causes amyotrophic lateral sclerosis? [version 1; referees: 3

approved] F1000Research 2017, 6(F1000 Faculty Rev):371 (doi: 10.12688/f1000research.10476.1)

First published: 28 Mar 2017, 6(F1000 Faculty Rev):371 (doi: 10.12688/f1000research.10476.1)

Introduction

Amyotrophic lateral sclerosis (ALS) is an incurable condition, characterised by progressive degeneration of upper and lower motor neurons, resulting in paralysis and death from respiratory failure in a median of 2–3 years¹. Despite the poor prognosis, there is considerable variation in the survival rate, and up to 10% of people with ALS live for more than 8 years from first symptoms². Understanding what causes ALS or influences survival is crucial for the development of effective treatments.

The causes of ALS are largely unknown. Significant advances have been made in understanding the genetic and environmental components of the disease. In this report, we will explore what is known about why some people develop ALS and how the risk factors work together to cause the disease.

Epidemiological studies of ALS

The incidence of ALS is about 2 per 100,000 person-years, and the prevalence is about 5 per 100,000 persons³. Because of the low prevalence, the average primary care physician will see 1 person in their lifetime, a typical UK neurologist will diagnose about 2 people a year, while a tertiary referral centre will see more than 100 people. Despite the low incidence, however, ALS is not particularly infrequent. The lifetime risk is about 1 in 300 by the age of 85, with the risk increasing steadily, at least until about the eighth decade of life^{4,5}. This is very similar to the risk for multiple sclerosis in the UK⁶.

Tertiary referral centres see sufficient numbers of people that research studies will have adequate power for statistical analysis. However, there is a significant diagnostic delay in ALS, typically about a year, which seems to be independent of healthcare system and is probably related to low recognition by primary care physicians⁷. As a result, those attending specialist centres tend to be those with a better prognosis, who are younger, and who are more motivated^{8,9}. In contrast, population-based registers capture all cases in a defined catchment population, regardless of attendance at a specialist clinic. Such registers have provided valuable insights into the epidemiology of ALS and offer an unbiased view of the condition¹⁰.

ALS can affect people at any age. The mean age of onset is 56 in clinic registers but 70 in population-based registers. In clinic registers, ALS is more frequent in men, with a male:female ratio of about 3:2, and the ratio becomes more equal with increasing age. In population registers, although the male preponderance is still seen, the ratio may be closer to 1:1, an effect that can be attributed to the greater capture of older people with ALS³.

What is ALS?

ALS presents in many different ways (Table 1), and it has been recognised for many years that the different clinical presentations correspond with differences in survival^{11,12}. Bulbar palsy, in which dysarthria followed by swallowing difficulty is the main presentation, is associated with the worst prognosis, and flail arm or flail leg

Table 1. Clinical presentations of amyotrophic lateral sclerosis.

Classifying feature	Name of phenotype	Description	
Motor neuron involvement	Amyotrophic lateral sclerosis (ALS)	Mixture of upper and lower motor neuron signs on clinical examination. Degree of certainty of diagnosis based on El Escorial criteria. May involve up to all regions.	
	Primary lateral sclerosis or upper motor neuron predominant ALS	Clinical signs limited to upper motor neuron features. Generally slowly progressive but involving up to all regions. This phenotype is usually confirmed if there have been no lower motor neuron signs after 4 years.	
	Progressive muscular atrophy or lower motor neuron predominant ALS	Clinical signs limited to lower motor neuron features. Slightly slower progression but can involve all regions. This phenotype is usually confirmed if there have been no upper motor neuron signs after 4 years.	
Site of onset	Bulbar onset	Site of onset may be included in the description of ALS, as different	
	Spinal onset	disease onset patterns have different rates of progression. The two categories are bulbar and spinal.	
Disease focality	Progressive bulbar palsy	Condition involving the bulbar region and predominantly lower motor neurons. May progress to other regions.	
	Pseudobulbar palsy	Condition involving the bulbar region and predominantly upper motor neurons. May progress to other regions.	
	Flail arm	Predominantly lower motor neuron proximal symmetrical involvement in the upper limbs. Some upper motor neuron signs may be seen in the lower limbs.	
	Flail leg	Lower motor neuron distal symmetrical involvement restricted to the lower limbs. May affect one side only.	
Cognitive involvement	ALS with cognitive impairment	ALS with some cognitive involvement below the threshold criteria for frontotemporal dementia.	
	ALS with frontotemporal dementia (ALS-FTD)	ALS with frank frontotemporal dementia.	

syndrome, in which there is symmetrical, predominantly flaccid weakness of the limbs, is associated with the best prognosis¹³. Perhaps surprisingly, statistical methods such as latent class cluster analysis can analyse the same data and identify different clinical subtypes that predict prognosis with far more discrimination than can neurologist classifications¹³. Most cases of ALS are focal in onset and relentlessly progressive, often to contiguous regions, although there are some exceptions¹⁴. The spread could be the result of a "prion-like" spread of toxic proteins through phagocytosis (consumption of cells by other cells) or possibly through a time-to-failure model^{15–17}. Lower motor neuron failure is the main cause of weakness in ALS and can be measured non-invasively to provide data to assess cellular patterns of spread¹⁸. Understanding the mechanisms of spread will aid the development of novel therapeutics and may aid models of prognosis.

The diagnosis of ALS is clinical, with the support of electrophysiological studies and the exclusion of mimics. In some cases, early diagnosis can be challenging, particularly if weakness is confined to one region for some time or is confined to a subset of motor neurons (upper only or lower only). A sensitive set of electrodiagnostic criteria, the Awaji criteria, can be particularly useful in the early diagnosis of people with bulbar onset disease, which is important because of the need for sooner gastrostomy when swallowing is affected early^{19–22}.

ALS is classified for research purposes by the El Escorial criteria and their revisions, which improve homogeneity in recruitment for clinical trials and other clinical studies^{23–26}. ALS progression is measured functionally using the ALS Functional Rating Scale – Revised, which uses 12 questions scored between 0 (no function) and 4 (full function) to generate a summary score²⁷. The scale is widely used but has some limitations, since the subscores correlate more accurately with progression in different clinical subtypes²⁸.

Disease staging allows a simple description of the extent of physical or functional involvement in an affected person and guides management. Such systems have been in widespread use in cancer for years. In ALS, two recent staging systems have been proposed: King's clinical staging and Milano-Torino staging (MiToS)^{29,30}. The King's system is similar to cancer staging in that the clinical spread of disease is used to infer the extent of disease progression. Spread is defined as involvement producing signs or symptoms in the El Escorial domains (1 domain is stage 1, 2 domains is stage 2, and 3 domains is stage 3), with respiratory or nutritional failure characterising stage 4. The ALS functional rating scale can be used to estimate the King's stage with 92% correlation³¹. MiToS uses the ALS functional rating scale subscores to define functional stage²⁹. Each system has benefits in describing ALS stage succinctly. The two disease staging systems are complementary³². King's staging summarises the clinical or anatomical spread of disease. Mapping disease progression to clinical stage rather than survival could be used as a secondary endpoint in clinical trials, which would shorten trial durations and provide meaningful information on which stage of the disease is prolonged by an effective therapy³³. MiToS summarises the functional burden of disease. It would therefore be useful in showing a functional benefit in clinical trials. Comparison of the systems shows that functional stage lags behind clinical stage, reflecting the functional reserve available in an affected limb, and it

has been proposed that a combined stage is used, as is standard in cancer, along the lines of K3M2, which would mean King's stage 3, MiToS stage 2^{32,34} (Figure 1).

It is now recognised that ALS involves non-motor systems³⁵. Between 30 and 50% of people have cognitive impairment detectable on formal testing, resulting from involvement of the frontotemporal circuits^{36,37}. Frank frontotemporal dementia occurs in about 5%, and in some families, people may have ALS, frontotemporal dementia, or both^{36,38,39}. The clinical impact of frontotemporal impairment in ALS is now more easily recognised because of recent advances in the tools available to detect it, such as the Edinburgh cognitive assessment score (ECAS)40,41. Other neurodegenerative diseases have also been linked to ALS, including spinocerebellar ataxia, in which case studies have reported the cooccurrence of ALS and cerebellar degeneration⁴². Schizophrenia may be more frequent in families with ALS, and there may also be an increased frequency of multiple sclerosis^{43,44}. In many of these cases, genetic factors are responsible for some of the risk. For example, pathological expansion of a repeat sequence in the C9orf72 gene is associated with ALS, frontotemporal dementia, or both, and the same mutation may increase the risk of schizophrenia, Parkinson's disease, and multiple sclerosis⁴⁵. Expansion of a repeat sequence in the ATXN2 gene is associated with ALS or, if more than 30 repeats are involved, with spinocerebellar ataxia⁴⁶. Autonomic, skin, and eye movement changes are also seen. Thus, ALS is a neurodegenerative disease in which the brunt falls on the motor system, but, as for many other neurodegenerations, the clinical syndrome is also dispersed through other anatomical and physiological systems.

Understanding prognostic factors in ALS

Respiratory impairment is usually an end-stage event in ALS. Despite this, because respiratory function is difficult to measure reliably with non-invasive methods, measurement of respiratory function is generally used as a guide to the use of respiratory support rather than prognostication⁴⁷. There have been many attempts at prognostic modelling, using either clinical features alone or biological markers such as albumin, creatinine, or neurofilament levels^{48,49}. Most studies find that longer survival is associated with younger age at symptom onset, presentation with limb dysfunction rather than swallowing or speech disturbance, and specific forms of ALS such as symmetrical patterns (e.g. flail arm syndrome) or upper motor neuron predominant forms⁵⁰. Conversely, cognitive impairment comprising executive dysfunction, rapid weight loss, and respiratory involvement at first examination, although not necessarily respiratory onset, predict a poor prognosis^{51–58}. The best predictor of slow progression, however, appears to be a long interval between symptom onset and diagnosis, probably because this reflects the rate of disease progression overall⁵⁹. Genetic variations have been associated with survival duration, with the best studied being variation in the UNC13A gene^{60,61}. Variation in the CAMTA1 gene has also been associated with survival⁶². Furthermore, some risk genes harbour variants that are themselves predictors of prognosis. For example, the p.Asp91Ala variation of the SOD1 gene is associated with very slow progression^{63,64}, while the p.Ala5Val variant is associated with aggressive disease⁶⁵. Statistical models can be used to provide clinically useful information for patients, the strongest message

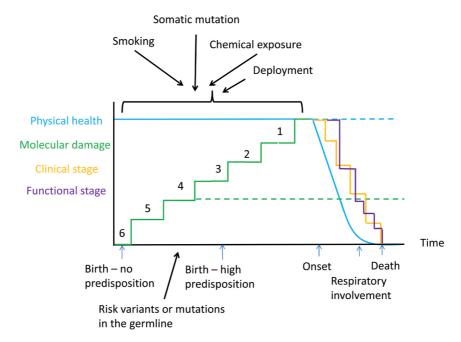


Figure 1. The time course of amyotrophic lateral sclerosis (ALS). Time is represented along the x-axis; physical health and molecular damage are represented along the y-axis. With time, molecular damage increases in a step-wise way until it reaches a threshold, at which point physical health declines, representing disease onset. People with a family history of ALS may have a large genetic predisposition to ALS and so need fewer steps to reach the level of molecular damage that causes disease, corresponding to a younger age of onset. Lack of exposure to sufficient risk factors means that the disease does not manifest, even if a genetic cause is present, explaining reduced penetrance. There is not a 1:1 mapping of risk factors and steps, as the steps represent molecular hits that lead to cellular damage rather than actual exposures. Once physical symptoms have started, progression shows a log-linear decline until the onset of respiratory symptoms, where decline is exponential. Clinical and functional involvement can be measured by the King's clinical staging and Milano-Torino staging (MiToS) systems. A dotted line represents the hypothetical trajectory in an unaffected individual. Black arrows represent genetic and environmental risk factors. Numbers indicate remaining molecular hits until disease onset.

being that survival is extremely unreliably predicted in individuals, even though patterns can be seen in the data^{\$4,57,66-68}.

Genetics and ALS

There are now more than 25 genes in which an association with ALS has been replicated, with the rate of gene discovery doubling every 4 years (http://alsod.iop.kcl.ac.uk)69. In up to 10% of people, there is a family history of ALS in a first-degree relative, but detailed genealogical studies extending to more distant relatives and including related diagnoses suggest that more than 20% have a relevant family history. The genes responsible for familial ALS have now been identified for about 70% of all cases, but there is a significant genetic component, even in those without a family history. Twin studies suggest the heritability is about 60%, and nearly every familial ALS gene has also been implicated in apparently sporadic ALS^{70,71}. Furthermore, statistical analysis shows that the distinction between familial and sporadic ALS is not clearcut, and large-scale genome-wide association studies (GWAS) show that the genetic architecture of sporadic ALS is one in which rare variation, more usually associated with familial disease, is disproportionately important^{72,73}.

The most recent GWAS of ALS identified four new associations, three of which were successfully replicated⁷³. An interesting feature of the study was that even though this was a study of

people with apparently sporadic ALS, there were associations in genes previously identified from family-based studies - C9orf72, TBK1, and NEK1 – further supporting the notion that familial and sporadic ALS are not mutually exclusive categories but rather a spectrum^{74–76}. These three genes all harbour variants that are moderately penetrant. In other words, carrying a disease-associated variant does not mean ALS will inevitably follow. Current thinking is that common diseases are the consequence of the additive effects of small increases in risk from multiple common variations (polygenic), and rare diseases are the consequence of single gene variants that are themselves rare but have a large effect on the probability of disease (monogenic). For example, height and schizophrenia are polygenic traits, while Huntington's disease and Kennedy's disease are monogenic diseases. ALS sits somewhere between these two extremes, with a lifetime prevalence that is far greater than is typical for a monogenic disease but far less than a common disease, and it is perhaps, therefore, to be expected that its genetic architecture also seems to sit somewhere between polygenic effects and monogenic high-penetrance disease.

There are three genes that have had a major impact on our understanding of ALS. ALS-linked dominant mutations in the superoxide dismutase gene *SOD1* were first identified in 1993, and since then mutations have been found in every exon of the gene⁷⁷. The SOD1

protein is a free radical scavenger, and loss of function, increasing free radical damage in cells, is a logical hypothesis to consider. However, several well-characterised SOD1 variants do not lead to a reduction in dismutase activity, and the evidence instead supports a toxic gain of function⁷⁸. Transgenic *SOD1* mice develop a motor neuron degeneration and have been used to model the disease for treatment development⁷⁹. The second important ALS gene is TAR-DBP, which codes for TDP-43, a protein regulating RNA expression and the major component of intracellular inclusions in ALS. The discovery of ALS-linked mutations in this gene was the first of many showing RNA processing defects to be important in ALS pathogenesis and, importantly, showed that the TDP-43 inclusions were not simply a passive marker of neuronal death but a crucial part of the disease pathway^{80–82}. The third important genetic finding in ALS was of linkage^{83,84} and then association^{85–87} of a locus on chromosome 9, which led researchers to the identification of a massive expansion of a hexanucleotide repeat in intron 1 of the C9orf72 gene^{88,89}. This is the most frequent cause of ALS, being responsible for about 30% of familial and up to 10% of sporadic

The focus of genetic research in ALS in the immediate future is therefore on rare variation. This is best discovered through highthroughput sequencing, and this technique has already identified several familial ALS genes. The major challenge facing researchers is how to interpret the findings, since the identification of a rare variant in an ALS gene is not in itself strong evidence of relevance in that individual, and over-representation of rare variation in cases over controls in a particular gene does not provide sufficient information for genetic counselling on a specific variant⁹⁰. The amount of heritability explained by genetic information captured on genomewide microarrays is about 12%, implying that the remainder is in rare variants and other types of genetic variation such as copy number variation, microsatellite repeats, post-transcriptional RNA editing, and epigenetic changes⁹¹. These are likely to be the next targets of ALS genetics research and are reliant on international research consortia. Project MinE is one such global collaboration that aims to analyse DNA from at least 15,000 people with ALS and 7,500 controls (https://www.projectmine.com/).

Environmental risk factors

In contrast to genetics, environmental risk factors for ALS have been more difficult to identify. Such studies are expensive to perform but difficult to fund and are heavily reliant on recall⁹². As a result, they are susceptible to bias. Furthermore, unlike genome-wide analyses, in which a hypothesis-generating approach can be taken, it is not straightforward to assay all possible environmental factors, and so a selected subset of assumed risk factors is tested. Smoking has been associated with increased risk of ALS in some studies and may hold a higher risk in some subgroups⁹³. Occupation, particularly military service with deployment, has been associated with risk of ALS, but the evidence mainly comes from the US, where there are large military datasets⁹⁴. Physical activity is another widely studied risk factor, partly because of a number of high-profile sports players who have had ALS and because of people with ALS having a low BMI on presentation and higher levels of leisure sports participation⁹⁵. It is not clear whether having higher levels of physical activity raises the risk of ALS and, if it does, whether it is the activity itself or being genetically predisposed to high sporting prowess that is the mechanism⁹⁶. Similarly, electric shock is not a risk factor in some analyses but is in others^{97,98}. There is mixed evidence for the

involvement of chemicals, such as heavy metals, ambient aromatic hydrocarbons, pesticides, and cyanotoxins^{99–103}. Trauma, including head injury, also appears to be a risk factor in meta-analysis¹⁰⁴.

Inflammation and ALS

Evidence of an immuno-inflammatory component in ALS pathogenesis is compelling ^{105,106}. A pathological hallmark of the neuroinflammation is prominent microglia activation at involved sites. T-regulatory lymphocytes (Tregs) are important immunomodulatory cells that regulate the balance between activation and suppression of the immune response and control the microglia in the central nervous system: specifically, pushing them towards a state in which remodeling and repair activities are activated. Defects in Treg levels or function have been found in ALS patients, becoming more frequent as the disease progresses. Treg levels are inversely correlated with disease severity, so that lower levels are seen in more severe disease, and survival is worse in those with Treg defects ^{105–109}. Studies are now underway to explore immune therapies that might improve Treg function and therefore improve survival.

Retroviruses and ALS

Poliovirus and other enteroviruses can cause a post-infectious myelitis with subsequent paralysis, and HIV infection can result in an ALS-like syndrome. Studies of serum and cerebrospinal fluid from ALS patients suggested that an activated endogenous retrovirus was associated with ALS¹¹⁰. Recently, the sequence has been identified as possibly HERV-K, an endogenous retrovirus that exists as an open reading frame in the human genome¹¹¹. In mice, the *env* protein component of HERV-K is toxic to motor neurons. There is no evidence that HERV-K is causative of the disease in humans, but studies are now underway to explore if antiretrovirals might slow progression and improve survival in ALS.

Conclusion

The apparently homogeneous phenotype of predominantly motor degeneration that is ALS can result from many different causes: genetic, epigenetic, environmental, and internal. Thus, many different pathways converge on the final outcome of upper and lower motor neuron death. Careful analysis of incidence data in European population registers shows that, on average, each pathway comprises six molecular steps¹¹² (see Figure 1). The model explains many otherwise enigmatic features of ALS, such as the increasing risk with age, genetic pleiotropy (the same gene variation can result in different diseases), age-dependent penetrance of disease genes, the difficulty in identifying a single environmental cause, the observation that ALS appears to start in one region and spread, and that it is specific to motor neurons but can affect other cell types. The next challenge is to understand the extent to which the pathways overlap and therefore might be amenable to a common treatment strategy. Although ALS remains a uniformly fatal diagnosis, accelerating advances in our understanding bring the hope that an effective treatment can be found for this devastating disease.

Competing interests

The authors declare that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

- Talbot K: Motor neuron disease: the bare essentials. Pract Neurol. 2009; 9(5): 303–09.
 - PubMed Abstract | Publisher Full Text
- Pupillo E, Messina P, Logroscino G, et al.: Long-term survival in amyotrophic lateral sclerosis: a population-based study. Ann Neurol. 2014; 75(2): 287–97.
 PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Chiò A, Logroscino G, Traynor BJ, et al.: Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology. 2013; 41(2): 118–30.
 Publided Abstract | Publisher Full Text | Free Full Text
- Alonso A, Logroscino G, Jick SS, et al.: Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. Eur J Neurol. 2009; 16(6): 745–51.
 PubMed Abstract | Publisher Full Text | Free Full Text
- Johnston CA, Stanton BR, Turner MR, et al.: Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. J Neurol. 2006; 253(12): 1642–43.
 PubMed Abstract | Publisher Full Text
- Alonso A, Hernán MA: Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008; 71(2): 129–35.
 PubMed Abstract | Publisher Full Text | Free Full Text
- Mitchell JD, Callagher P, Gardham J, et al.: Timelines in the diagnostic evaluation of people with suspected amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)-a 20-year review: can we do better? Amyotroph Lateral Scler. 2010; 11(6): 537–41.
 - PubMed Abstract | Publisher Full Text
- Lee JR, Annegers JF, Appel SH: Prognosis of amyotrophic lateral sclerosis and the effect of referral selection. J Neurol Sci. 1995; 132(2): 207–15.
 PubMed Abstract | Publisher Full Text
- Sorenson EJ, Mandrekar J, Crum B, et al.: Effect of referral bias on assessing survival in ALS. Neurology. 2007; 68(8): 600–2.
 PubMed Abstract | Publisher Full Text
- Logroscino G, Traynor BJ, Hardiman O, et al.: Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. J Neurol Neurosurg Psychiatry. 2008; 79(1): 6–11.
 PubMed Abstract | Publisher Full Text
- Al-Chalabi A, Hardiman O, Kiernan MC, et al.: Amyotrophic lateral sclerosis: moving towards a new classification system. Lancet Neurol. 2016; 15(11): 1182–94.
 - PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Wolf J, Safer A, Wöhrle JC, et al.: Variability and prognostic relevance of different phenotypes in amyotrophic lateral sclerosis - data from a populationbased registry. J Neurol Sci. 2014; 345(1-2): 164-67.
 PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Wijesekera LC, Mathers S, Talman P, et al.: Natural history and clinical features
 of the flail arm and flail leg ALS variants. Neurology. 2009; 72(12): 1087–94.
 PubMed Abstract | Publisher Full Text | Free Full Text
- Ravits JM, La Spada AR: ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. Neurology. 2009; 73(10): 805–11.
 - PubMed Abstract | Publisher Full Text | Free Full Text
- 15. F Bidhendi EE, Bergh J, Zetterström P, et al.: Two superoxide dismutase prion strains transmit amyotrophic lateral sclerosis-like disease. J Clin Invest. 2016; 126(6): 2249–53.
 PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Clarke G, Lumsden CJ, McInnes RR: Inherited neurodegenerative diseases: the one-hit model of neurodegeneration. Hum Mol Genet. 2001; 10(20): 2269–75.
 PubMed Abstract
- Liu G, Fiala M, Mizwicki MT, et al.: Neuronal phagocytosis by inflammatory macrophages in ALS spinal cord: inhibition of inflammation by resolvin D1. Am J Neurodegener Dis. 2012; 1(1): 60–74.
 PubMed Abstract | Free Full Text
- Nandedkar SD, Barkhaus PE, Stalberg EV: Motor unit number index (MUNIX): principle, method, and findings in healthy subjects and in patients with motor neuron disease. Muscle Nerve. 2010; 42(5): 798–807.
 PubMed Abstract | Publisher Full Text
- Atassi N, Cudkowicz ME, Schoenfeld DA: Advanced statistical methods to study the effects of gastric tube and non-invasive ventilation on functional decline and survival in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2011; 12(4): 272–77.
 - PubMed Abstract | Publisher Full Text | Free Full Text
- Costa J, Swash M, de Carvalho M: Awaji criteria for the diagnosis of amyotrophic lateral sclerosis:a systematic review. Arch Neurol. 2012; 69(11): 1410–16.
 - PubMed Abstract | Publisher Full Text
- Geevasinga N, Menon P, Loy C, et al.: Revisiting early diagnosis in ALS. Clin Neurophysiol. 2016; 127(3): e13–e14.
 Publisher Full Text
- 22. F Geevasinga N, Menon P, Scherman DB, et al.: Diagnostic criteria in

- amyotrophic lateral sclerosis: A multicenter prospective study. *Neurology.* 2016; **87**(7): 684–90.
- PubMed Abstract | Publisher Full Text | F1000 Recommendation
- 23. Brooks BR: El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci. 1994; 124(Suppl): 96–107.
 - PubMed Abstract | Publisher Full Text | F1000 Recommendation
- de Carvalho M, Dengler R, Eisen A, et al.: Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008; 119(3): 497–503.
 PubMed Abstract | Publisher Full Text
- Miller RG, Munsat TL, Swash M, et al.: Consensus guidelines for the design and implementation of clinical trials in ALS. World Federation of Neurology committee on Research. J Neurol Sci. 1999; 169(1-2): 2-12.
 PubMed Abstract | Publisher Full Text
- Schrooten M, Smetcoren C, Robberecht W, et al.: Benefit of the Awaji diagnostic algorithm for amyotrophic lateral sclerosis: a prospective study. Ann Neurol. 2011; 70(1): 79–83.
 PubMed Abstract | Publisher Full Text
- 27. F Cedarbaum JM, Stambler N, Malta E, et al.: The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999; 169(1–2): 13–21. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- 28. F Rooney J, Burke T, Vajda A, et al.: What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2016. pii: jnnp-2016-314661. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Chiò A, Hammond ER, Mora G, et al.: Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2015; 86(1): 38–44.
 PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Roche JC, Rojas-Garcia R, Scott KM, et al.: A proposed staging system for amyotrophic lateral sclerosis. Brain. 2012; 135(Pt 3): 847–52.
 PubMed Abstract | Publisher Full Text | Free Full Text
- Balendra R, Jones A, Jivraj N, et al.: Estimating clinical stage of amyotrophic lateral sclerosis from the ALS Functional Rating Scale. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15(3–4): 279–84.
 PubMed Abstract | Publisher FullText
- Fang T, Al Khleifat A, Stahl DR, et al.: Comparison of the King's and MiToS staging systems for ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2017. 1–6.
 - PubMed Abstract | Publisher Full Text
- Balendra R, Jones A, Jivraj N, et al.: Use of clinical staging in amyotrophic lateral sclerosis for phase 3 clinical trials. J Neurol Neurosurg Psychiatry. 2015; 86(1): 45–9.
 - PubMed Abstract | Publisher Full Text
- Ferraro D, Consonni D, Fini N, et al.: Amyotrophic lateral sclerosis: a comparison of two staging systems in a population-based study. Eur J Neurol. 2016; 23(9): 1426–32.
 - PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Swinnen B, Robberecht W: The phenotypic variability of amyotrophic lateral sclerosis. Nat Rev Neurol. 2014; 10(11): 661–70.
 PubMed Abstract | Publisher Full Text
- 36. Montuschi A, lazzolino B, Calvo A, et al.: Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. J Neurol Neurosurg Psychiatry. 2015; 86(2): 168–73.
- PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Rippon GA, Scarmeas N, Gordon PH, et al.: An observational study of cognitive impairment in amyotrophic lateral sclerosis. Arch Neurol. 2006; 63(3): 345–52.
 - PubMed Abstract | Publisher Full Text
- Lomen-Hoerth C, Anderson T, Miller B: The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. Neurology. 2002; 59(7): 1077–9.
 PubMed Abstract | Publisher Full Text
- Strong MJ: The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2008; 9(6): 323–38.
 PubMed Abstract | Publisher Full Text
- Abrahams S, Newton J, Niven E, et al.: Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2014; 15(1–2): 9–14.
 - PubMed Abstract | Publisher Full Text
- 41. F Niven E, Newton J, Foley J, et al.: Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): A cognitive tool for motor disorders. Amyotroph Lateral Scler Frontotemporal Degener. 2015; 16(3–4): 172–79.
 - PubMed Abstract | Publisher Full Text | F1000 Recommendation

- Tazen S, Figueroa K, Kwan JY, et al.: Amyotrophic lateral sclerosis and spinocerebellar ataxia type 2 in a family with full CAG repeat expansions of ATXN2. JAMA Neurol. 2013; 70(10): 1302-4.
 PubMed Abstract | Publisher Full Text | Free Full Text
- Etemadifar M, Abtahi SH, Akbari M, et al.: Multiple sclerosis and amyotrophic lateral sclerosis: is there a link? *Mult Scler.* 2012; **18**(6): 902–4. PubMed Abstract | Publisher Full Text
- Howland RH: Schizophrenia and amyotrophic lateral sclerosis. Compr Psychiatry. 1990; 31(4): 327-36. PubMed Abstract | Publisher Full Text
- Cooper-Knock J, Shaw PJ, Kirby J: The widening spectrum of C90RF72related disease; Genotype/phenotype correlations and potential modifiers of clinical phenotype. Acta Neuropathol. 2014; 127(3): 333–45.
 PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- F Neuenschwander AG, Thai KK, Figueroa KP, et al.: Amyotrophic lateral sclerosis risk for spinocerebellar ataxia type 2 ATXN2 CAG repeat alleles: a meta-analysis. JAMA Neurol. 2014; 71(12): 1529–34. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Polkey MI, Lyall RA, Yang K, et al.: Respiratory Muscle Strength as a Predictive Biomarker for Survival in Amyotrophic Lateral Sclerosis. Am J Respir Crit Care Med. 2017; 195(1): 86-95. PubMed Abstract | Publisher Full Text | Free Full Text
- F Chiò A, Calvo A, Bovio G, et al.: Amyotrophic lateral sclerosis outcome measures and the role of albumin and creatinine: a population-based study. JAMA Neurol. 2014; 71(9): 1134–42. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Lu CH, Macdonald-Wallis C, Gray E, et al.: Neurofilament light chain: A prognostic biomarker in amyotrophic lateral sclerosis. Neurology. 2015; 84(22): 2247-57 PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- F Calvo A, Moglia C, Lunetta C, et al.: Factors predicting survival in ALS: a multicenter Italian study. J Neurol. 2016; 264(1): 54–63.
 PubMed Abstract | Publisher Full Text | F1000 Recomm
- Elamin M, Phukan J, Bede P, et al.: Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology. 2011; **76**(14): 1263–9. PubMed Abstract | Publisher Full Text
- Marin B, Arcuti S, Jesus P, et al.: Population-Based Evidence that Survival in Amyotrophic Lateral Sclerosis is Related to Weight Loss at Diagnosis. Neurodegener Dis. 2016; 16(3–4): 225–34. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Moura MC, Novaes MR, Eduardo EJ, et al.: Prognostic Factors in Amyotrophic Lateral Sclerosis: A Population-Based Study. PLoS One. 2015; 10(10): e0141500.
 - PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Wolf J, Safer A, Wöhrle JC, et al.: Factors Predicting Survival in ALS Patients--Data from a Population-Based Registry in Rhineland-Palatinate, Germany. Neuroepidemiology. 2015; 44(3): 149-55. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Wolf J, Safer A, Wöhrle JC, et al.: Factors predicting one-year mortality in amyotrophic lateral sclerosis patients--data from a population-based registry. BMC Neurol. 2014; 14(1): 197. PubMed Abstract | Publisher Full Text | Free Full Text
- Czaplinski A, Yen AA, Appel SH: Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry.* 2006; **77**(3): 390–2. PubMed Abstract | Publisher Full Text | Free Full Text
- Knibb JA, Keren N, Kulka A, et al.: A clinical tool for predicting survival in ALS. J Neurol Neurosurg Psychiatry. 2016; 87(12): 1361-1367. PubMed Abstract | Publisher Full Text | Free Full Text
- Shoesmith CL, Findlater K, Rowe A, et al.: Prognosis of amyotrophic lateral sclerosis with respiratory onset. J Neurol Neurosurg Psychiatry. 2007; 78(6):
 - PubMed Abstract | Publisher Full Text | Free Full Text
- Czaplinski A, Yen AA, Appel SH, et al.: Amyotrophic lateral sclerosis: early predictors of prolonged survival. *J Neurol.* 2006; **253**(11): 1428–36. PubMed Abstract | Publisher Full Text
- Diekstra FP, van Vught PW, van Rheenen W, et al.: UNC13A is a modifier of survival in amyotrophic lateral sclerosis. Neurobiol Aging. 2012; 33(3): 630.e3-8. PubMed Abstract | Publisher Full Text
- Gaastra B, Shatunov A, Pulit S, et al.: Rare genetic variation in UNC13A may modify survival in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2016; 17(7–8): 593–99.

 PubMed Abstract | Publisher Full Text | Free Full Text
- Fogh I, Lin K, Tiloca C, et al.: Association of a Locus in the CAMTA1 Gene With Survival in Patients With Sporadic Amyotrophic Lateral Sclerosis. JAMA Neurol. 2016; 73(7): 812-20. PubMed Abstract | Publisher Full Text
- Andersen PM, Al-Chalabi A: Clinical genetics of amyotrophic lateral sclerosis: what do we really know? Nat Rev Neurol. 2011; 7(11): 603–15. PubMed Abstract | Publisher Full Text

- Andersen PM, Nilsson P, Ala-Hurula V, et al.: Amyotrophic lateral sclerosis associated with homozygosity for an Asp90Ala mutation in CuZn-superoxide dismutase. Nat Genet. 1995; 10(1): 61-6. PubMed Abstract | Publisher Full Text
- $\hbox{Cudkowicz ME, McKenna-Yasek D, Sapp PE, } \textit{et al.:} \textbf{Epidemiology of mutations in}$ superoxide dismutase in amyotrophic lateral sclerosis. Ann Neurol. 1997; 41(2): 210-21. PubMed Abstract | Publisher Full Text
- Taylor AA, Fournier C, Polak M, et al.: Predicting disease progression in 66. amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2016; 3(11): 866–75. PubMed Abstract | Publisher Full Text | Free Full Text
- Sato Y, Nakatani E, Watanabe Y, et al.: Prediction of prognosis of ALS: Importance of active denervation findings of the cervical-upper limb area and trunk area. Intractable Rare Dis Res. 2015; 4(4): 181-9. PubMed Abstract | Publisher Full Text | Free Full Text
- Carreiro AV, Amaral PM, Pinto S, et al.: Prognostic models based on patient snapshots and time windows: Predicting disease progression to assisted ventilation in Amyotrophic Lateral Sclerosis. *J Biomed Inform.* 2015; **58**: 133–44. PubMed Abstract | Publisher Full Text
- Olubunmi A. Al-Chalabi A: ALSoD: Amvotrophic Lateral Sclerosis Online Genetics Database.
- Al-Chalabi A, Fang F, Hanby MF, et al.: An estimate of amyotrophic lateral sclerosis heritability using twin data. J Neurol Neurosurg Psychiatry. 2010; 81(12): 1324-26. PubMed Abstract | Publisher Full Text | Free Full Text
- Al-Chalabi A, Lewis CM: Modelling the effects of penetrance and family size on rates of sporadic and familial disease. Hum Hered. 2011; 71(4): 281-88. PubMed Abstract | Publisher Full Text
- Majounie E, Renton AE, Mok K, et al.: Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012; 11(4): 323-30. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- van Rheenen W, Shatunov A, Dekker AM, et al.: Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. Nat Genet. 2016; 48(9): 1043-48. PubMed Abstract | Publisher Full Text
- Chiò A, Borghero G, Restagno G, et al.: Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of C9orf72. Brain. 2012; 135(Pt 3): 784-93. PubMed Abstract | Publisher Full Text | Free Full Text
- Kenna KP, van Doormaal PT, Dekker AM, et al.: NEK1 variants confer susceptibility to amyotrophic lateral sclerosis. Nat Genet. 2016; 48(9): 1037–42. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Williams KL, McCann EP, Fifita JA, et al.: Novel TBK1 truncating mutation 76 in a familial amyotrophic lateral sclerosis patient of Chinese origin. Neurobiol Aging. 2015; 36(12): 3334.e1-34.e5. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Rosen DR, Siddique T, Patterson D, et al.: Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993; 362(6415): 59-62. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- F Kaur SJ, McKeown SR, Rashid S: Mutant SOD1 mediated pathogenesis of Amyotrophic Lateral Sclerosis. Gene. 2016; 577(2): 109-18. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Cleveland DW, Bruijn LI, Wong PC, et al.: Mechanisms of selective motor neuron death in transgenic mouse models of motor neuron disease. *Neurology.* 1996; 47(4 Suppl 2): S54–61; discussion S61–2. PubMed Abstract | Publisher Full Text
- Lagier-Tourenne C, Polymenidou M, Hutt KR, et al.: Divergent roles of ALSlinked proteins FUS/TLS and TDP-43 intersect in processing long pre-mRNAs. Nat Neurosci. 2012; 15(11): 1488-97. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Van Deerlin VM, Leverenz JB, Bekris LM, et al.: TARDBP mutations in amyotrophic lateral sclerosis with TDP-43 neuropathology: a genetic and histopathological analysis. Lancet Neurol. 2008; 7(5): 409–16. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Sreedharan J. Blair IP. Tripathi VB. et al.: TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. Science. 2008; 319(5870): 1668-72. PubMed Abstract | Publisher Full Text
- Vance C, Al-Chalabi A, Ruddy D, et al.: Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2–21.3. Brain. 2006; 129(Pt 4): 868-76. PubMed Abstract | Publisher Full Text
- Morita M, Al-Chalabi A, Andersen PM, et al.: A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. Neurology. 2006; 66(6): 839-44.
 - PubMed Abstract | Publisher Full Text
- Laaksovirta H, Peuralinna T, Schymick JC, et al.: Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study. Lancet Neurol. 2010; 9(10): 978-85. PubMed Abstract | Publisher Full Text | Free Full Text

- 86. Shatunov A, Mok K, Newhouse S, et al.: Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. Lancet Neurol. 2010; 9(10): 986–94.
 PubMed Abstract | Publisher Full Text | Free Full Text
- van Es MA, Veldink JH, Saris CG, et al.: Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis. Nat Genet. 2009; 41(10): 1083–7.
 - PubMed Abstract | Publisher Full Text
- 88. F Renton AE, Majounie E, Waite A, et al.: A hexanucleotide repeat expansion in C9orf72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011; 72(2): 257–68.
 PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- 89. F DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al.: Expanded GGGGCC hexanucleotide repeat in noncoding region of C9orf72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011; 72(2): 245–56.
 PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Kosmicki JA, Churchhouse CL, Rivas MA, et al.: Discovery of rare variants for complex phenotypes. Hum Genet. 2016; 135(6): 625–34.
 PubMed Abstract | Publisher Full Text
- McLaughlin RL, Vajda A, Hardiman O, et al.: Heritability of Amyotrophic Lateral Sclerosis: Insights From Disparate Numbers. JAMA Neurol. 2015; 72(8): 857–57.
 - PubMed Abstract | Publisher Full Text | F1000 Recommendation

 Al-Chalabi A, Hardiman O: The epidemiology of ALS: a conspiracy of genes,
- environment and time. Nat Rev Neurol. 2013; 9(11): 617–28.

 PubMed Abstract | Publisher Full Text

 93 Along A Logressing G Hornén MA: Smeking and the risk of amyetrophic
- Alonso A, Logroscino G, Hernán MA: Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2010; 81(11): 1249–52.
 PubMed Abstract | Publisher Full Text
- 94. F Beard JD, Kamel F, et al.: Military Service, Deployments, and Exposures in Relation to Amyotrophic Lateral Sclerosis Etiology and Survival. Epidemiol Rev. 2015; 37(1): 55–70.
- PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

 Scarmeas N, Shih T, Stern Y, et al.: Premorbid weight, body mass, and varsity
- Scarmeas N, Shih T, Stern Y, et al.: Premorbid weight, body mass, and varsity athletics in ALS. Neurology. 2002; 59(5): 773–5.
 PubMed Abstract | Publisher Full Text
- 96. Lacorte E, Ferrigno L, Leoncini E, et al.: Physical activity, and physical activity related to sports, leisure and occupational activity as risk factors for ALS: A systematic review. Neurosci Biobehav Rev. 2016; 66: 61–79. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- 97. Abhinav K, Al-Chalabi A, Hortobagyi T, et al.: Electrical injury and amyotrophic lateral sclerosis: a systematic review of the literature. J Neurol Neurosurg Psychiatry. 2007; 78(5): 450–53.

 PubMed Abstract | Publisher Full Text | Free Full Text
- 98. Fischer H, Kheifets L, Huss A, et al.: Occupational Exposure to Electric Shocks and Magnetic Fields and Amyotrophic Lateral Sclerosis in Sweden. Epidemiology. 2015; 26(6): 824–30.

 PubMed Abstract | Publisher Full Text | F1000 Recommendation
- 99. F Bozzoni V, Pansarasa O, Diamanti L, et al.: Amyotrophic lateral sclerosis

- and environmental factors. Funct Neurol. 2016; 31(1): 7–19.

 PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation
- Delzor A, Couratier P, Boumédiène F, et al.: Searching for a link between the L-BMAA neurotoxin and amyotrophic lateral sclerosis: a study protocol of the French BMAALS programme. BMJ Open. 2014; 4(8): e005528.
 PubMed Abstract | Publisher Full Text | Free Full Text
- 101. Rooney J, Vajda A, Heverin M, et al.: No association between soil constituents and amyotrophic lateral sclerosis relative risk in Ireland. Environ Res. 2016; 142: 102-7.
 - PubMed Abstract | Publisher Full Text | F1000 Recommendation
- 102. Sutedja NA, Veldink JH, Fischer K, et al.: Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: a systematic review. Amyotroph Lateral Scler. 2009; 10(5–6): 302–9. PubMed Abstract | Publisher Full Text
- Malek AM, Barchowsky A, Bowser R, et al.: Exposure to hazardous air pollutants and the risk of amyotrophic lateral sclerosis. Environ Pollut. 2015; 197: 181–6.
- PubMed Abstract | Publisher Full Text | F1000 Recommendation

 24. Wang MD, Little J, Gomes J, et al.: Identification of risk factors associated with
- 104. Wang MD, Little J, Gomes J, et al.: Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology. 2016; pii: S0161-813X(16)30116-4. PubMed Abstract | Publisher Full Text
- Evans MC, Couch Y, Sibson N, et al.: Inflammation and neurovascular changes in amyotrophic lateral sclerosis. Mol Cell Neurosci. 2013; 53: 34–41.
 PubMed Abstract | Publisher Full Text
- 106. Zhao W, Beers DR, Appel SH: Immune-mediated mechanisms in the pathoprogression of amyotrophic lateral sclerosis. J Neuroimmune Pharmacol. 2013; 8(4): 888–99. PubMed Abstract | Publisher Full Text | Free Full Text
- Henkel JS, Beers DR, Wen S, et al.: Regulatory T-lymphocytes mediate amyotrophic lateral sclerosis progression and survival. EMBO Mol Med. 2013; 5(1): 64–79.
 PubMed Abstract | Publisher Full Text | Free Full Text
- Mantovani S, Garbelli S, Pasini A, et al.: Immune system alterations in sporadic amyotrophic lateral sclerosis patients suggest an ongoing neuroinflammatory process. J Neuroimmunol. 2009; 210(1–2): 73–79.
 PubMed Abstract | Publisher Full Text
- 109. Rentzos M, Evangelopoulos E, Sereti E, et al.: Alterations of T cell subsets in ALS: A systemic immune activation? Acta Neurol Scand. 2012; 125(4): 260–64. PubMed Abstract | Publisher Full Text
- McCormick AL, Brown RH Jr, Cudkowicz ME, et al.: Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. Neurology. 2008; 70(4): 278–83.
 PubMed Abstract | Publisher Full Text
- 111. F Li W, Lee MH, Henderson L, et al.: Human endogenous retrovirus-K contributes to motor neuron disease. Sci Transl Med. 2015; 7(307): 307ra153. PubMed Abstract | Publisher Full Text | F1000 Recommendation
- Al-Chalabi A, Calvo A, Chio A, et al.: Analysis of amyotrophic lateral sclerosis as a multistep process: a population-based modelling study. Lancet Neurol. 2014; 13(11): 1108–13.
 - PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current	Referee	Status:	/	•	

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

- Mamede de Carvalho Institute of Physiology, Faculty of Medicine, University of Lisbon, Lisbon, Portugal; Department of Neurosciences, Hospital de Santa Maria, Lisbon, Portugal Competing Interests: No competing interests were disclosed.
- 2 Richard W Orrell University College London Institute of Neurology, London, UK Competing Interests: No competing interests were disclosed.
- 3 Robert P. Bowser Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Pheonix, USA

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

