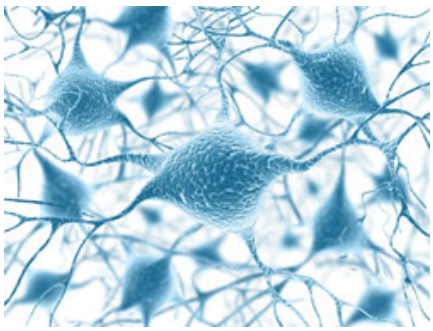
MOTOR NEURON DISEASE II

Pathophysiology, genetics, proteins, therapies

Bernard Schneider
October 2024



Lecture plan

1. **Motor system**
   - Overview
2. **Motor Neuron Diseases**
   - Clinical presentation
   - Molecular pathology
3. **Amyotrophic Lateral Sclerosis**
   - Clinical presentation, epidemiology, etiology
   - Molecular pathology: RNA metabolism
   - Non-cell autonomous mechanisms

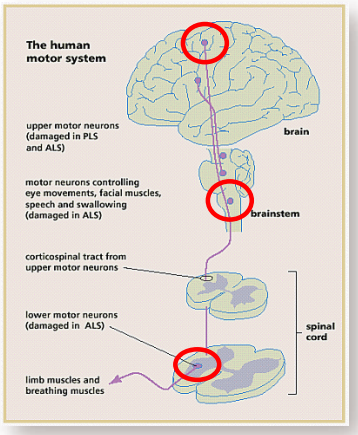
Motor neuron diseases: Amyotrophic Lateral Sclerosis

- Lou Gehrig's disease
- motoneuron degeneration in motor cortex, brain stem and spinal cord
- no cure
- first described by Jean-Martin Charcot (1869)

"a" for without
"myo" for muscle
"trophic" for nourishment
"lateral" for side (of the spinal cord)
"sclerosis" for hardening or scarring in area following deterioration

J.M. Charcot

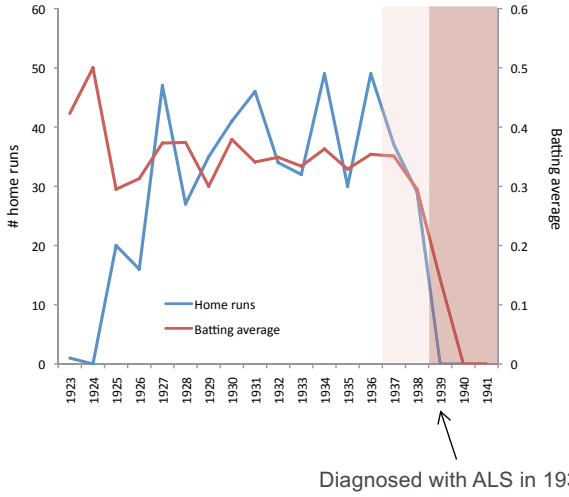
Lou Gehrig



Motor neuron diseases: ALS

Lou Gehrig – New York Yankee baseball player

1903 - 1941

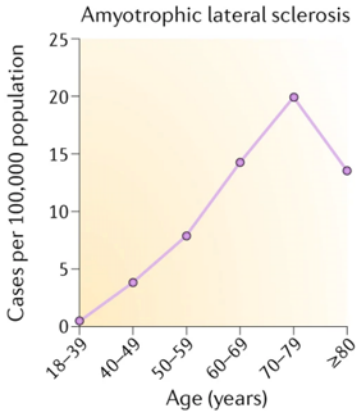


Diagnosed with ALS in 1939

Motor neuron diseases: ALS

Epidemiology of ALS

- Most common motor neuron disorder
  - Incidence: 1.5 - 2.7 in 100,000
  - Prevalence: 2.7 - 7.4 in 100,000
  - Lifetime risk: 1:400 – 1:2,000
  - >450,000 patients worldwide
- Mean age at onset: 56 yrs (rare cases < 20)
- Affects people 40 – 70 yrs old
- 120,000 people diagnosed each year worldwide
- 90% Caucasian
- Male:Female ratio 1.3 – 1.5:1 (mainly in young onset cases)



- *Nature Reviews Neurology volume 15, pages 565–581 (2019)*

Motor neuron diseases: ALS

Disease progression

- Rapid progression
- No remission
- Death from respiratory failure
- Median survival: 3-5 yrs
- 10% live ≥10 yrs

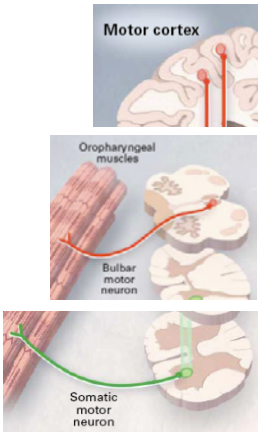
- Rare survival beyond 20 years

Stephen Hawking
(diagnosed in 1963)
1942-2018

Motor neuron diseases: ALS

Symptoms

Progression rate



Initial symptoms

Upper motor neuron →
- Stiffness (spasticity)
- Brisk tendon reflexes
- Abnormal reflexes
- Lack of coordination, dexterity

Bulbar motor neuron →
- Speech difficulty
- Swallowing difficulty
- Tongue fasciculation

Lower motor neuron →
- Respiratory muscle weakness
- Generalized weakness
- Twitching muscles (fasciculation)
- Asymmetric limb weakness
- Muscle cramps
- Foot drop

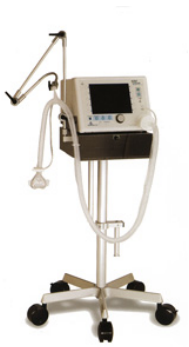
- the progression pattern suggests disease spread among contiguous pools of motor neurons

48

Motor neuron diseases: ALS

Clinical aspects of ALS

- By the time patients are given a definitive diagnosis of ALS they are usually wheelchair bound or require assistance feeding. It is estimated that they have already lost 60% of motoneurons
- Finding biomarkers is critical to allow for early intervention
- No cure available
- Available treatments: riluzole, radicava
- Locked-in
- Respiratory failure most common cause of death
  - Respiratory assistance

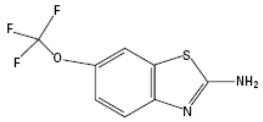


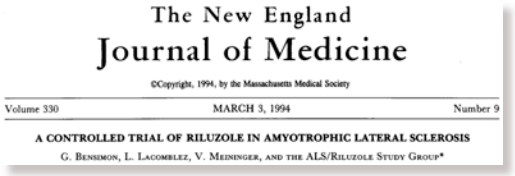
49

Motor neuron diseases: ALS

ALS: treatments

- Rilutek® (riluzole): FDA approved drug
- increases lifespan by **2 months** (well tolerated)
- Although riluzole reduces glutamate excitotoxicity in some models, its mode of action remains unclear.




The New England
Journal of Medicine
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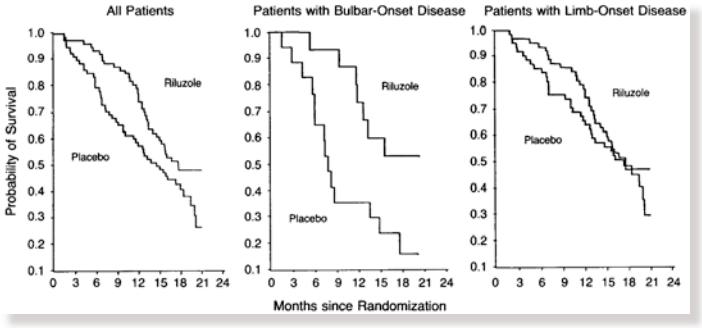
Volume 330 MARCH 3, 1994 Number 9
A CONTROLLED TRIAL OF RILUZOLE IN AMYOTROPHIC LATERAL SCLEROSIS
G. Bensimon, L. Lacomblez, V. Meininger, and the ALS/Riluzole Study Group*



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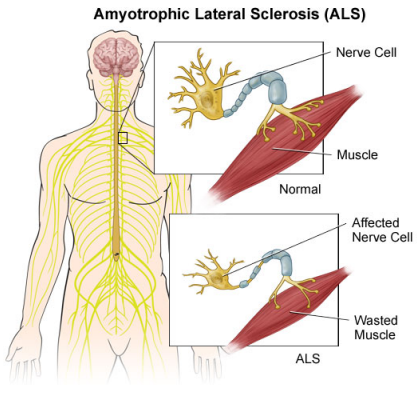
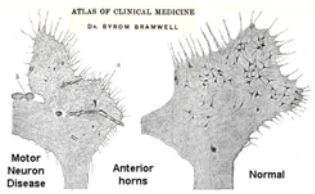
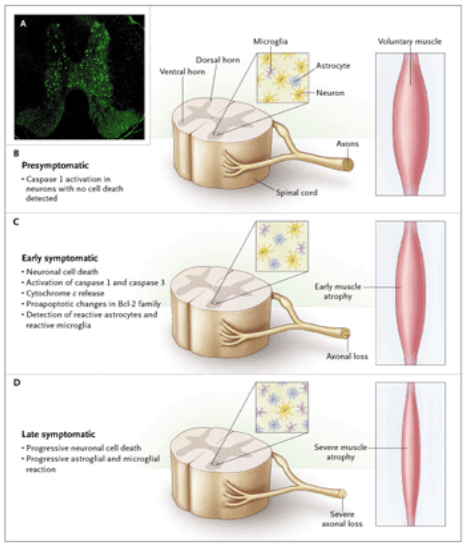
Motor neuron diseases: ALS

51

Pathology







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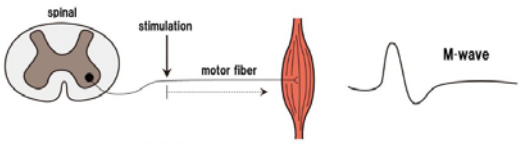
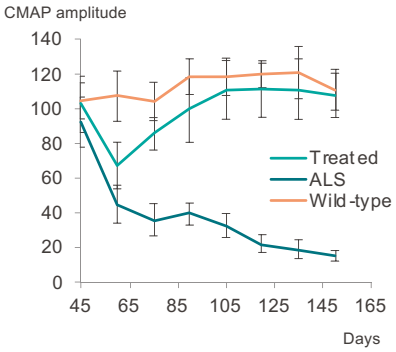
Motor neuron diseases: question 6

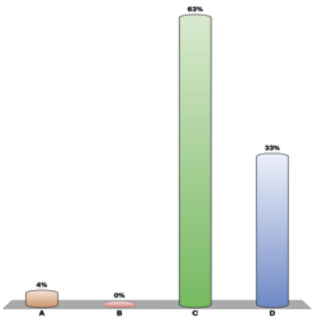
The following graph shows the monitoring of the compound muscle action potential (EMG) in a mouse model of amyotrophic lateral sclerosis.

How would you interpret the result in the treated group?





A. The treatment is fully protecting the neuromuscular function
B. There is no loss of motoneurons in the spinal cord, because the EMG is rescued
C. After a first loss of neuromuscular junctions, the remaining motoneurons reinnervate the muscle
D. The decrease in action potential amplitude reflects a transient atrophy of the muscle

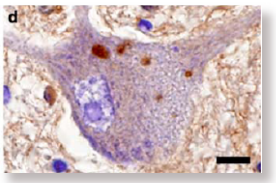


52

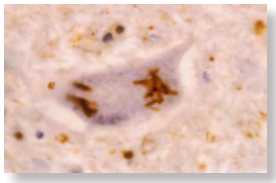
Motor neuron diseases: ALS

Protein pathology

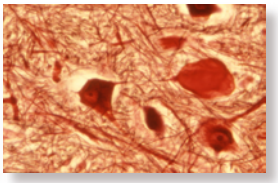
- Accumulation of phosphorylated neurofilaments
- Inclusion bodies (Bunina bodies and Lewy body-like)
- Ubiquitin-positive inclusions



Bunina bodies
(cytoplasmic proteinaceous inclusions)

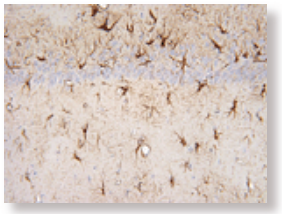


skein-like inclusions



axonal swelling

Astrogliosis
Microglial activation

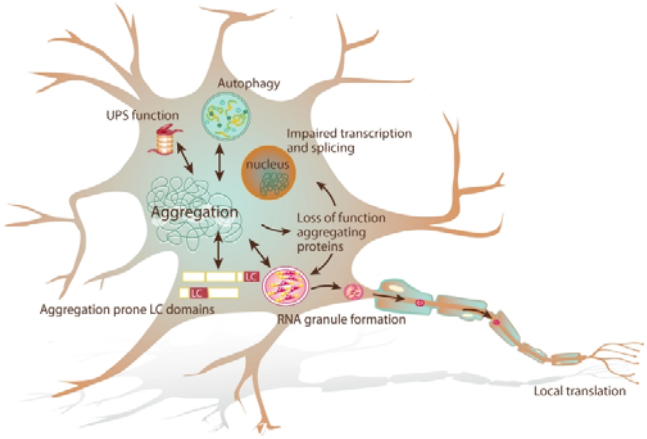


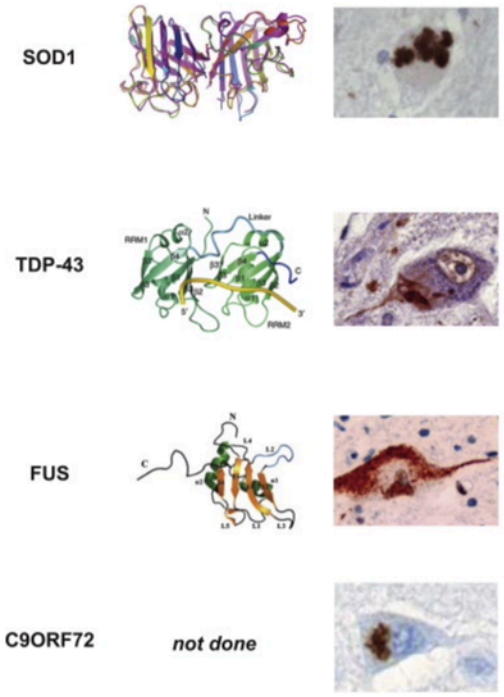
53

Motor neuron diseases: ALS

54

Protein pathology





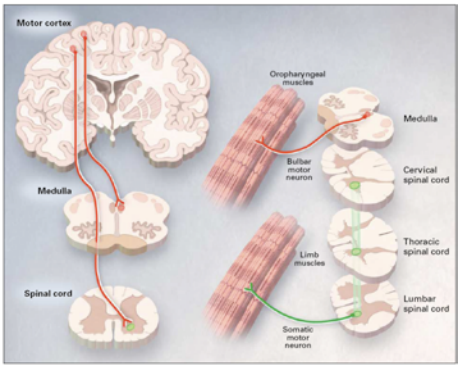
54

Motor neuron diseases: ALS

55

Selective vulnerability of motoneurons

- **Disease selectively affecting motor neurons**
- Cognitive dysfunction or decline is observed but remains a minor feature of the disease:
  - dementia reported in less than 15% of the ALS patients
  - cognitive impairment in >40% of patients



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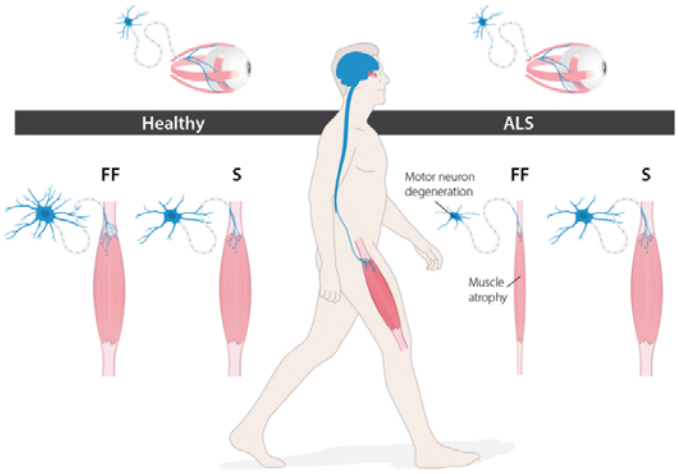
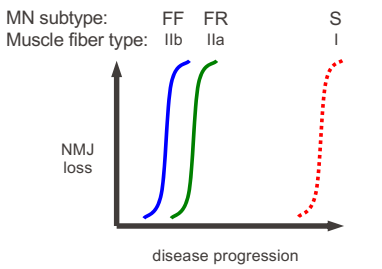
Motor neuron diseases: ALS

Vulnerable and resistant motor neurons



NMJ denervation by MN subtype
Pun S et al., Nat Neuroscience 2006



FF: fast-fatigable (strength)
FR: fatigue-resistant
S: slow (endurance)

- Nijssen, J., Comley, L.H. & Hedlund, E. Acta Neuropathol (2017) 133: 863.

Motor neuron diseases: question 7

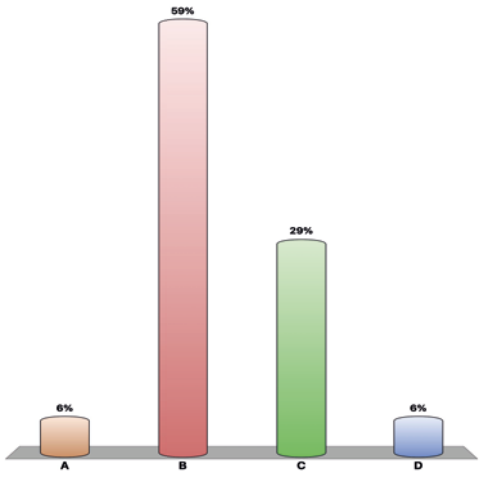
Researchers have compared the transcriptional profile of motoneurons that are resistant or vulnerable to disease. What is your opinion on this approach?

A. This is irrelevant as these pools of neurons differ in their integration in the local circuit

B. This is an effective approach to identify protective genes.

C. This approach may identify mechanisms that are inherent to motoneurons but will fail to identify possible cause of disease in muscle or glial cells.

D. The vulnerability of neurons is unlikely to be the same in humans and in animal models.

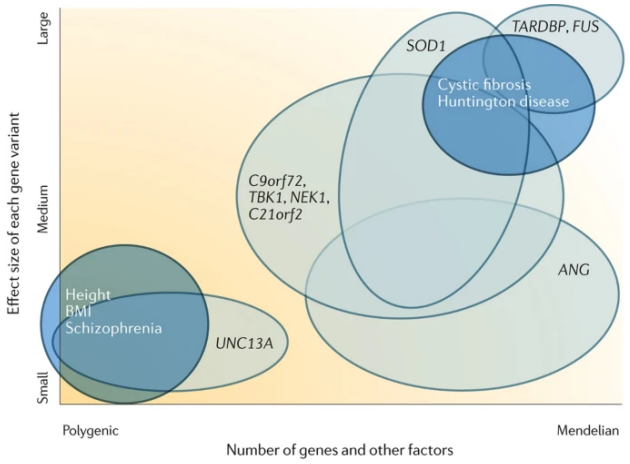


Etiology: genetic versus sporadic forms

Two forms, clinically indistinguishable

- Sporadic (sALS): 90% of all cases
- Familial (fALS): 10% of cases

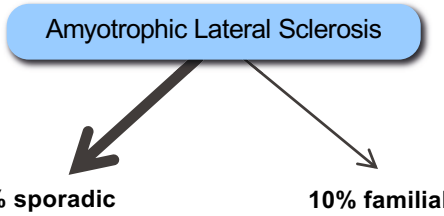
Mean age of onset: ***sALS > fALS***

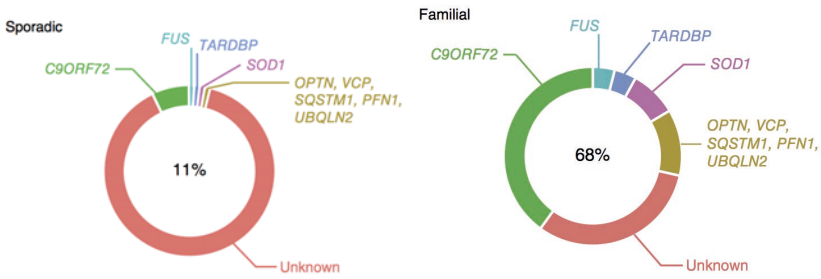


- *Nature Reviews Neurology volume 13, pages 96–104 (2017)*

- genetic cause identified in >70% of familial ALS cases
- genes include C9ORF72, SOD1, TDP43, FUS
- **gain of a toxic function (autosomal dominant inheritance)**
- Similar mechanisms might be involved in sporadic ALS

Genetics of ALS





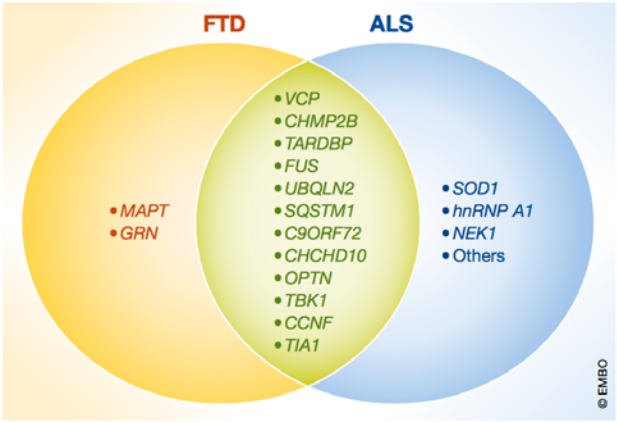
- Renton AE et al, Nat Neurosci 2014

fALS – non exhaustive list of genes that predispose to ALS

ALS disease type	Gene	Chromosome	Inheritance	Clinical features
Mendelian genes				
ALS1	***SOD1***	21q22.1	**AD**	Typical ALS
ALS2	*ALS2 (Alsin)*	2q33	AR	Juvenile onset, slowly progressive, predominantly corticospinal
ALS4	*SETX*	9q34	**AD**	Adult onset, slowly progressive
ALS6	***FUS***	16q12	**AD**	ALS, frontotemporal dementia
ALS8	*VAPB*	20q13.3	**AD**	Atypical ALS, slowly progressive with tremors
ALS9	*ANG*			
ALS10	***TDP43***	1p36.22	**AD**	Spinal onset, low motor neurons, frontotemporal dementia
ALS11	FIG4	6q21	**AD**	
ALS	OPTN	10	AR	
ALS-X	UBQLN2	X (centromere)	**XD**	Typical ALS
ALS-FTDP	Tau	17q21	**AD**	ALS, frontotemporal dementia + parkinsonism
ALS-FTD	***C9ORF72***	9p-21	**AD**	ALS, frontotemporal dementia
ALS(?)	*Dynactin*	2p13	**AD**	Adult onset, slowly progressive
Mendelian loci				
ALS3	?	18q21	**AD**	Typical ALS
ALS5	?	15q15-21	AR	Juvenile onset, slowly progressive
ALS7	?	20p13	**AD**	Typical ALS
ALS-FTD	?	9q21-22	**AD**	ALS, frontotemporal dementia
Mitochondrial genes				
ALS-M	COX1	mtDNA	Maternal	Single case, predominantly corticospinal
ALS-M	IARS2	mtDNA	Maternal	Single case, predominantly lower motor neuron

Motor neuron diseases: ALS

Genetics: ALS and frontotemporal dementia



- Gao FB et al, EMBO J 2017

Motor neuron diseases: ALS

Sporadic ALS: environmental factors

Risk factors:

- only established environmental risk factor: age

Putative risk factors:

- smoking

?

- heavy metal exposure (mercury, lead, aluminium)
- higher incidence in the first US Gulf War veterans
- service in US military
- being an Italian soccer player
- exposure to infectious agents
  - Mycoplasma (up to 80% of patients of ALS patients)
  - Borrelia burgdorferi

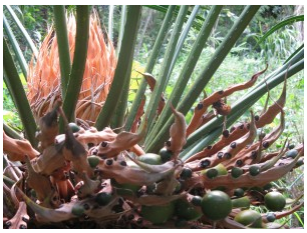
Motor neuron diseases: ALS

Sporadic ALS: environmental factors

Geographical clustering

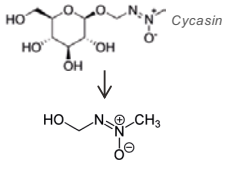
- Guam (Pacific ocean; US) – Chamorro people: epidemic in 1950s
- Kii peninsula (Japan)
- West New Guinea
- North Africa (juvenile ALS)
- Madras (India)

Lytico-bodig disease: characteristics of ALS and PD

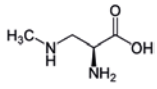


Cycas circinalis is used to produce flour

Mariana fruit bat (flying fox): accumulates BMAA in fat



[(Z)-methyl-ONN-azoxy]methanol (MAM)



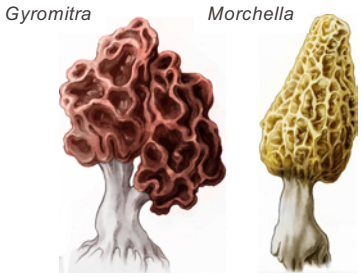
β-Methylamino-L-alanine (BMAA)

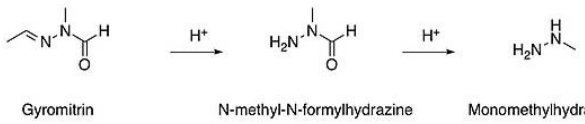
Exposure to cycas-derived toxins is considered a risk factor for ALS

Motor neuron diseases: ALS

Sporadic ALS: environmental factors

- Cluster of ALS cases caused by 'False Morel' consumption
- Hotspot of ALS in Savoie, in the Tarentaise Valley
- Incidence of ALS cases higher than normal
- 14 ALS cases between 1991 and 2013
- Genotoxic fungi





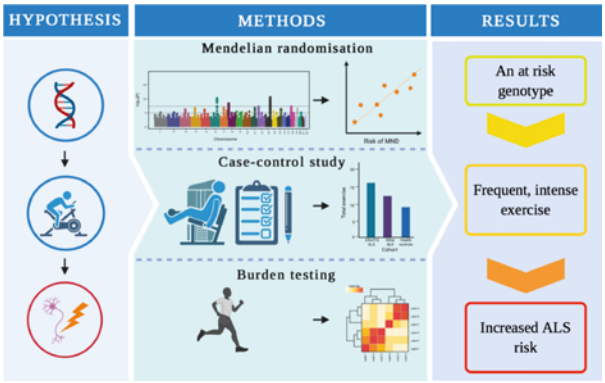
MMH metabolite similar to MAA
- affects GABA production
- ROS production
- DNA damage

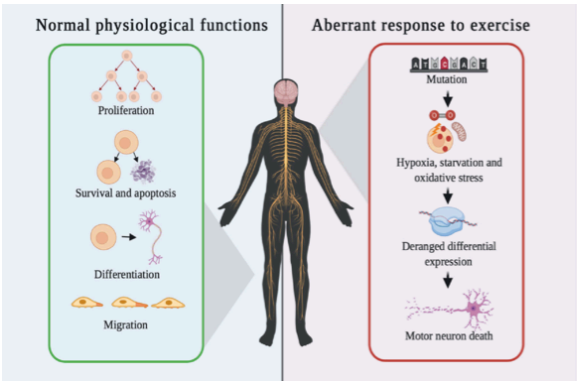
E. Lagrange, et al. J Neurol Sci, 427 (2021); https://doi.org/10.1016/j.jns.2021.117558.

Motor neuron diseases: ALS

Sporadic ALS: environmental factors

Is frequent and prolonged exercise a '<u>second hit</u>' in ALS?





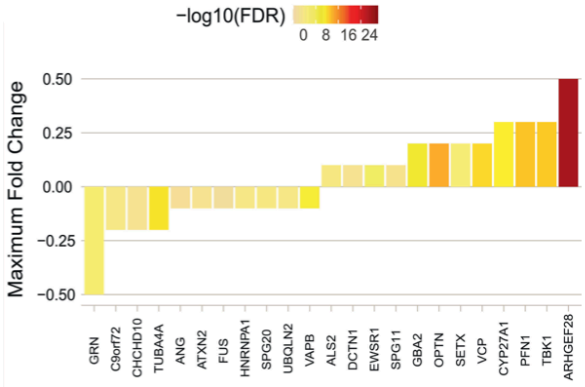
Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. TH Julian *et al*, Lancet 2021

Motor neuron diseases: ALS

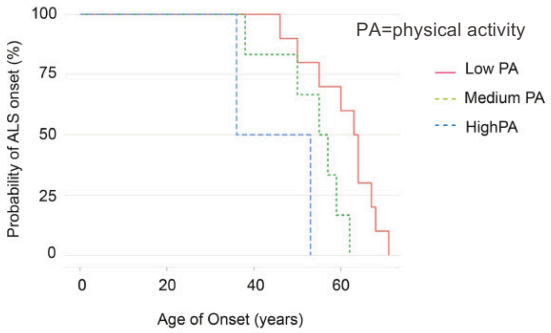
Sporadic ALS: environmental factors

Is frequent and prolonged exercise a ‘second hit’ in ALS?

ALS risk genes differentially expressed in response to exercise
(fold change and significance)



C9ORF72-ALS



- Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. TH Julian *et al*, Lancet 2021