

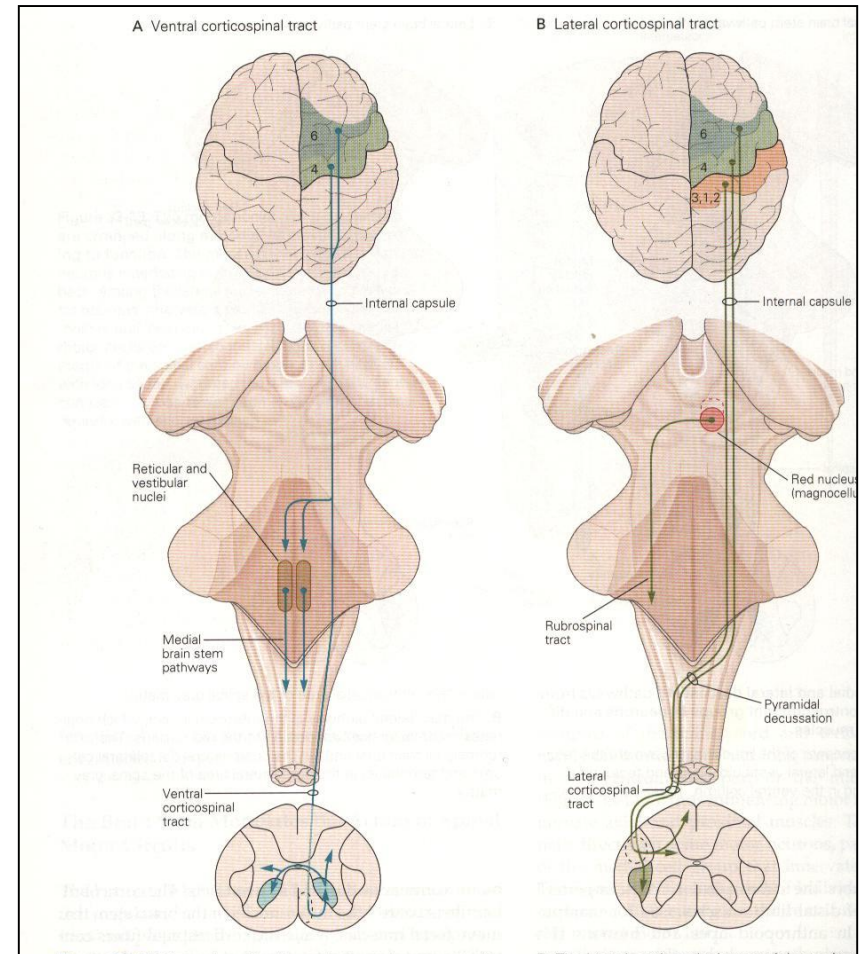


Enfermedades de neurona motora en el adolescente y el adulto

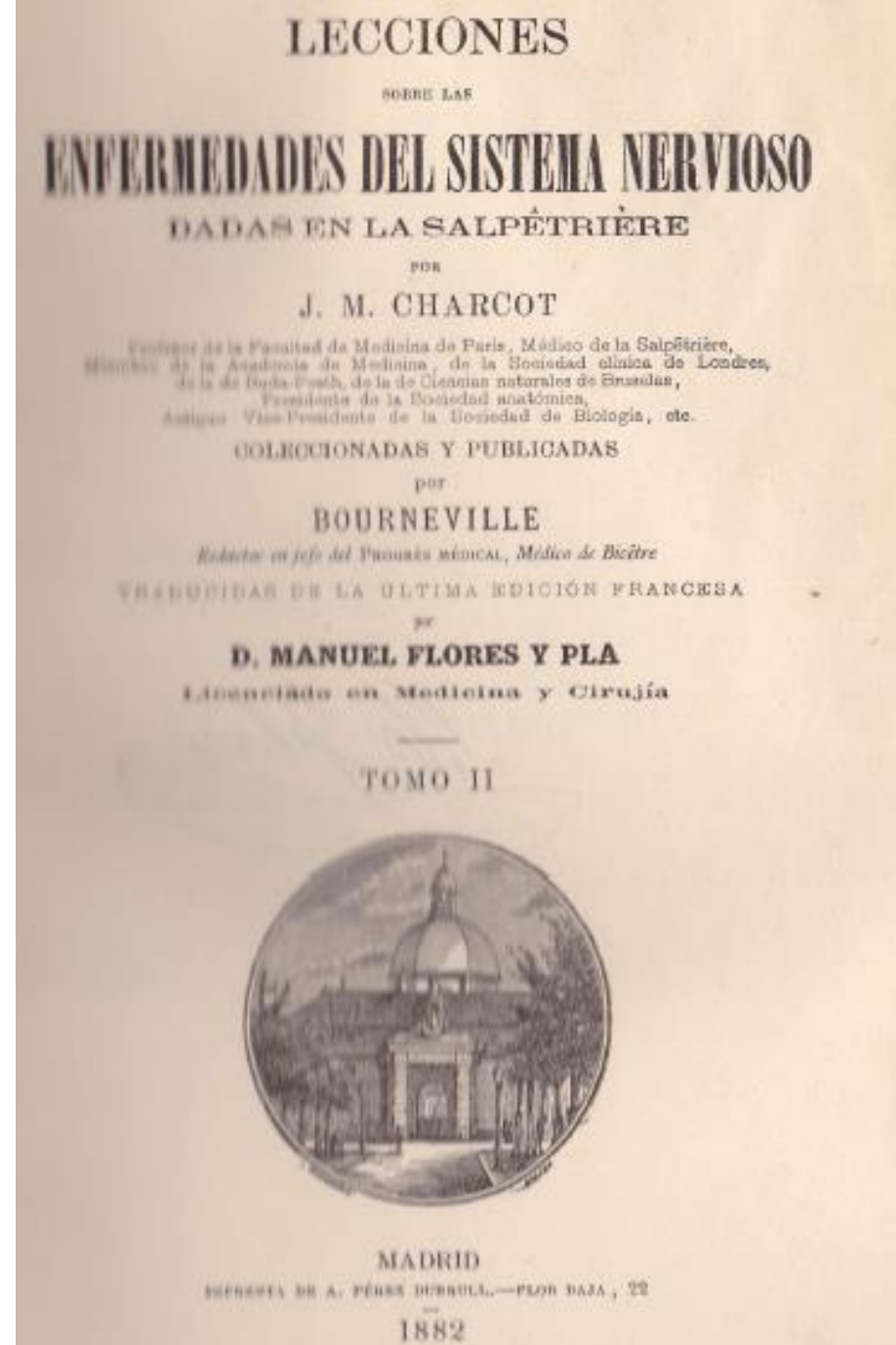
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Hospital Clínico San Carlos
Madrid

Enfermedades de neurona motora

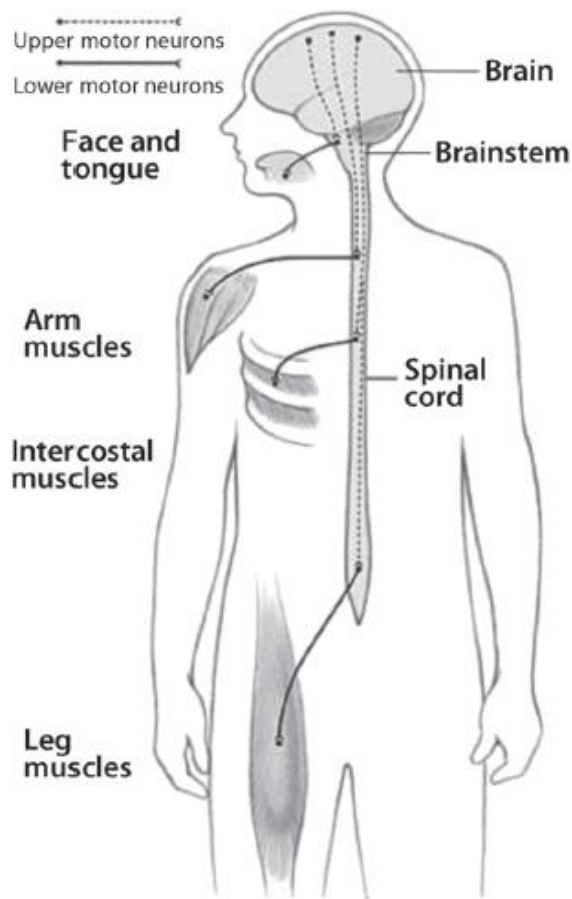
- Son un grupo de enfermedades clínica y patológicamente heterogéneo caracterizado por la degeneración progresiva de las motoneuronas.
- Las mas frecuentes: AME (SMA), ATROFIA BULBOESPINAL (Kennedy), ELA.



- J.M Charcot es quien describe por primera vez esta enfermedad como una entidad clinicopatológica en 1869.
 - Charcot J.M; Joffroy A: Deux cas d'atrophie musculaire progressive avec lésions de la substance grise et des faisceaux antéro-latéraux de la moelle épinière. Archives de physiologie normale et pathologique, 1869, pag.356



- Cataline Aubel entro en la Salpêtrière (clinica de Charcot) en el mes de junio de 1865....fallecio 11 de febrero de 1869.
- Isabelle P... de 58 años de edad entro en la Salpêtrière (clinica de Charcot) el 11 de julio de 1871...fallece 25 de octubre 1871.
 - Atrofia muscular progresiva marcada principalmente en los miembros superiores. Atrofia de los músculos de la lengua y del orbicular de los labios. Paralasis con rigidez de los miembros inferiores.
 - Atrofia o desaparición de las células nerviosas de los cuernos anteriores en las regiones cervical y dorsal. En el bulbo atrofia y destrucción de las células nerviosas del núcleo del hipogloso, atrofia de las raíces espinales anteriores y de las raíces del hipogloso y facial. Esclerosis acintada, simétrica de los cordones laterales.

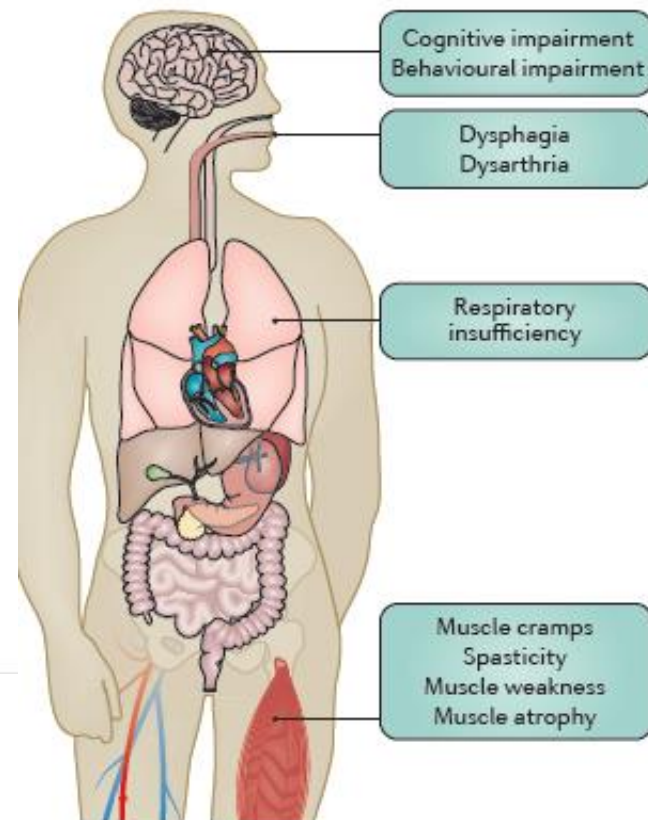


• Upper motor neuron signs

- Very little wasting
- Increased tone (spasticity)
- Brisk reflexes (hyperreflexia)
- Primitive reflexes (Babinski sign)

• Lower motor neuron signs

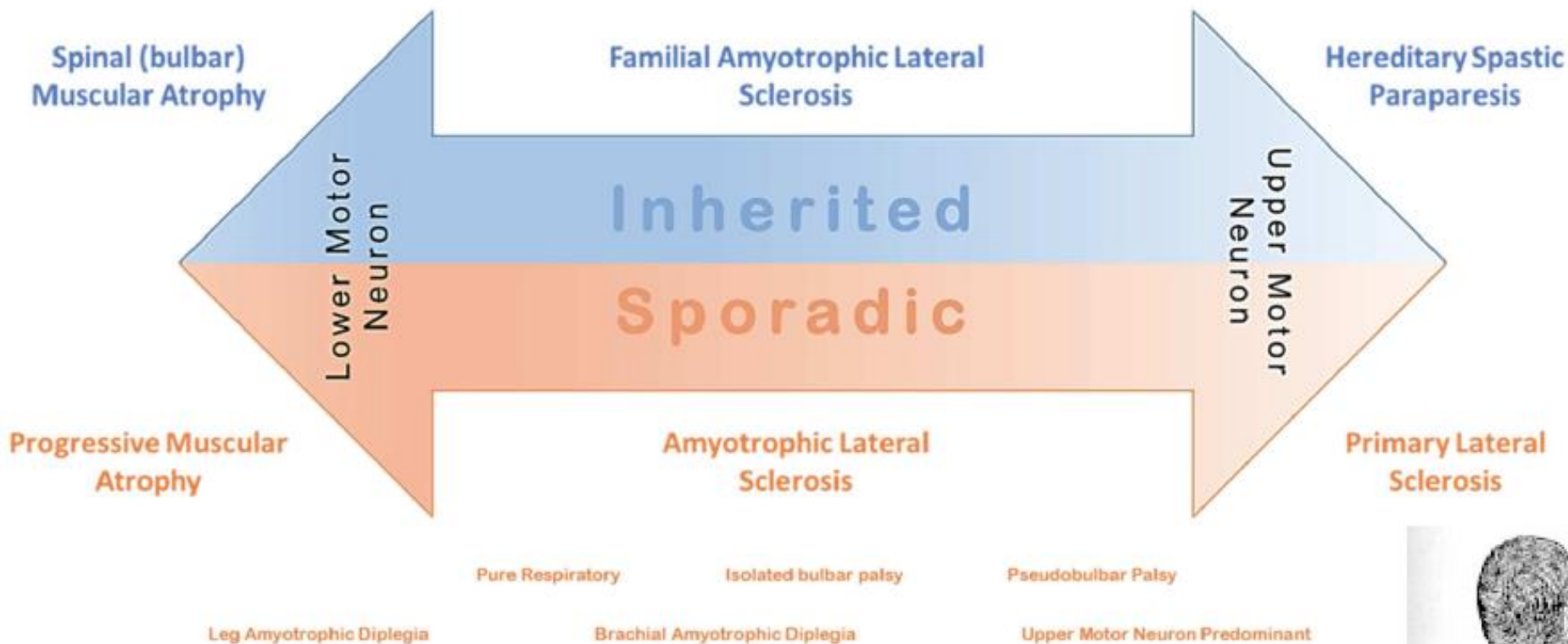
- Wasting (atrophy)
- Low or normal tone (flaccidity)
- Reduced or absent reflexes (hyporeflexia or areflexia)
- Fasciculations (low threshold for irritation of the motor neuron)



Continuum (Minneapolis) 2014;20(5):1185–1207.

Orla Hardiman, Ammar Al-Chalabi, Adriano Chio, Emma M. Corr, Giancarlo Logroscino, Wim Robberecht, Pamela J. Shaw, Zachary Simmons and Leonard H. van den Berg

Nature Reviews Disease Primers 3, 17071 (2017)



VARIANTES

Diplejía braquial amiotrofica (BAD)
 Diplejia crural amiotrofica (LAD)
 ELA bulbar aislada (IBALS)

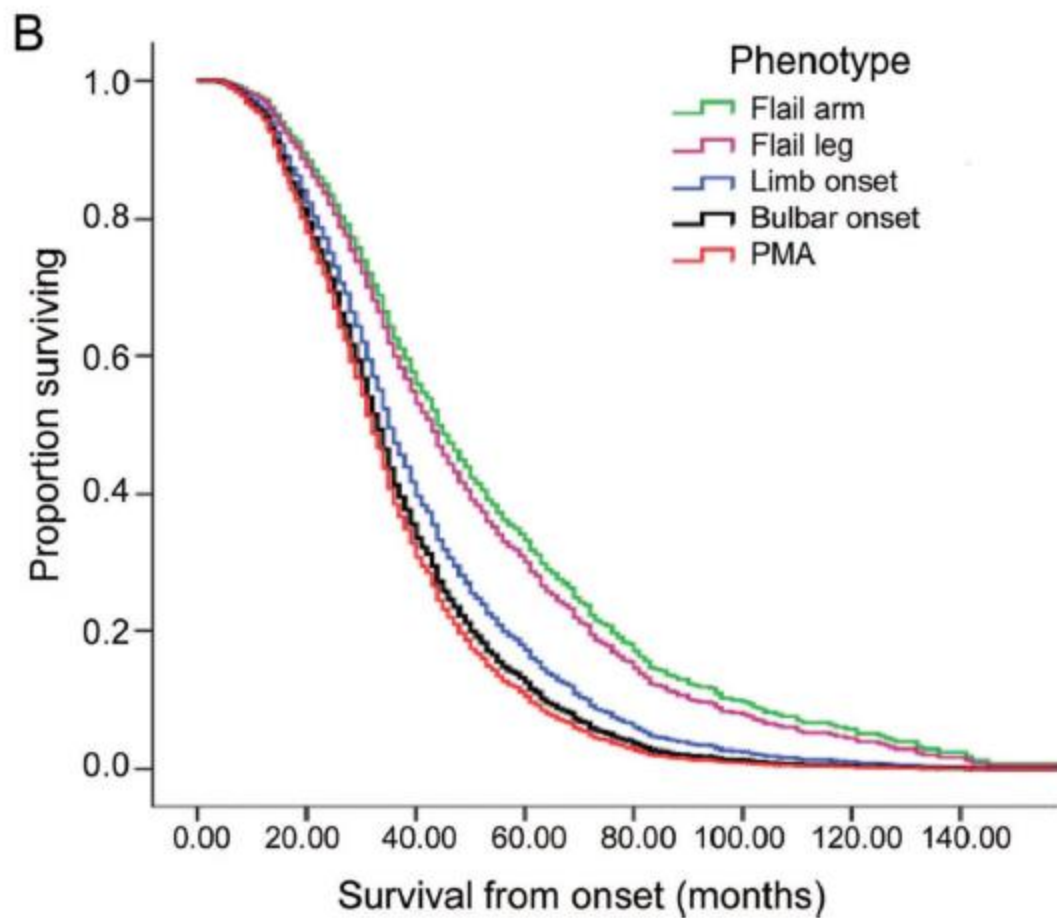
Esclerosis lateral amiotròfica

- Enfermedad neurodegenerativa
- Incidencia: 2-3/100.000 hab/año (EURALS)
- Prevalencia: 4-8 hab/100.000
 - 70-79 años 17/100.00 y 18-39 años 0,5/100.000

Edad media de aparición: 58 años (55-65), con intervalo amplio entre 15-90 años. (5% formas juveniles < 25 años)

ELA FAMILIAR 10 % DE LOS CASOS

- Más frecuente en varones (3:2), aunque parece ser mayor la incidencia masculina en paciente jóvenes y con una mayor afectación espinal.
- Deterioro cognitivo (DFT) hasta 50 % de los casos.
- Esperanza de vida 3 a 5 años, pero 20 % sobrevive 5 años y 10% 10 años o mas.



DIAGNOSTICO

- Sospecha clínica por signos de 2ª neurona motora + signos de 1ª neurona motora.
- Electromiografía
 - SIGNOS DE DENERVACION: FIBRILACIONES, OP, FASCICULACIONES.
 - PATRON DE MAXIMO ESFUERZO DISMINUIDO.
 - PUM AMPLITUD Y DURACION AUMENTADOS, POLIFASICOS.
- Neurografía motora y sensitiva normal.
- CK normal o elevadas (< 1000)
- LCR normal
- RM cráneo y espinal normal
- Histología muscular atrofia con reagrupamiento de fibras tipo I y tipo II.

Table 1: ALS diagnosis: List of differential diagnosis and clinical overlap with ALS

	Differential diagnosis of ALS	Clinical overlap with ALS	Diagnostic to rule in/out
Hereditary conditions	Spino bulbar muscular atrophy (KD)	Progressive motor neuron degeneration ^[91]	Genetic testing. Identification of disease-specific mutations such as the CAG repeat expansion in the androgen receptor in SBMA ^[231]
	Hereditary spastic paraparesis	Gait disturbance, lower extremity spasticity ^[188]	Genetic testing ^[90]
	Acid maltase deficiency	Respiratory failure and muscle weakness are common clinical presentations ^[194]	Respiratory function tests, including the maximal static respiratory pressures, electromyographic examination and histochemical and biochemical studies of muscle biopsy specimens ^[250]
	Facioscapulohumeral muscular dystrophy	Muscle weakness	Presents initially with a distinct pattern of weakness involving the facial and scapular stabilizer muscles, with varying descending progression to involve the distal anterior leg or hip-girdle muscles. This is usually a benign dystrophy, but 20% of patients involved in certain clinical trials eventually become wheelchair-bound
	Adrenomyeloneuropathy	X-linked inherited metabolic disorder causing demyelination ^[241]	Detection of abnormal accumulation of very long chain fatty acids in plasma or red cells ^[212]
	Huntington disease	Progressive motor disturbances and involuntary movements ^[147]	Genetic testing ^[231]
Metabolic conditions	Hexosaminidase deficiency	Tremor, dystonia, spastic paresis, and psychosis have been noted in individual cases ^[134]	β -hexosaminidase subunits α and β assay, ganglioside GM-1 and GM-2 antibodies ^[115]
	Metal intoxication (especially iron and mercury)	Motor neuron dysfunction ^[155]	Heavy metals panel ^[207]
	Lathyrism	Pyramidal pattern of motor weakness, spasticity, and increased tone in the extensors and adductors of the thigh, as well in the gastrocnemius muscles with a "lurching gait" ^[175]	Diagnosed based on specified symptom criteria, and if clinically indicated ^[112]
	Organophosphate toxic effects	Peripheral neuropathy, fasciculations ^[214]	History of exposure to organophosphates

	Differential diagnosis of ALS	Clinical overlap with ALS	Diagnostic to rule in/out
Immune and/or inflammatory conditions	Multifocal motor neuropathy with conduction block	Peripheral nerve disorder characterized by progressive and asymmetric limb weakness, usually of the upper extremities. Minor sensory disturbances may be present	Nerve conduction studies of multifocal persistent partial conduction blocks on motor but not sensory nerves ^[218]
	Chronic inflammatory demyelinating polyneuropathy	Acquired neuropathy with highly variable clinical presentation ^[256]	Various electrodiagnostic criteria to include assessment of the distal compound muscle action potential duration ^[288]
	Myasthenia gravis	Various presentation of fatigable muscle weakness, especially of the legs and extra-ocular movements	Presence of serum antibodies to acetylcholine receptor ^[309]
	Inclusion body myositis, polymyositis	Progressive muscle weakness and atrophy of the lower extremities	
	Multiple sclerosis	Episodic paresthesias and muscle weakness ^[15]	McDonald criteria, neuroimaging, spinal tap when clinically indicated ^[190]
Structural disorders	Cervical spondylotic myelopathy	Compression of the spinal cord that causes progressive neurologic deterioration ^[139]	Neuroradiologic imaging ^[86]
Neurodegenerative diseases	Corticobasal degeneration	Focal dystonia and myoclonia of the limbs, various clinical presentation and progression ^[99]	Current clinical diagnostic criteria under review ^[11]
	Multiple system atrophy	Sporadic neurodegenerative disorder with any combination of parkinsonian, autonomic, cerebellar, or pyramidal signs ^[321]	Indicated by cell loss, gliosis, and glial cytoplasmic inclusions in multiple CNS entities ^[321]
	Progressive supranuclear palsy	Extrapyramidal rigidity, bradykinesia, gait impairment, bulbar palsy, and dementia ^[82]	CT and MRI scans show midbrain atrophy early and later atrophy of the pontine and midbrain tegmentum and the frontal and temporal lobes. PET scans have shown frontal hypometabolism and loss of striatal D-2 dopamine receptors ^[82]
	Parkinson's disease	Progressive motor dysfunction and bradykinesia	Clinical presentation criteria based on stage of disease and response to various medications ^[37]

A

Revised El Escorial criteria

UMN + LMN
in 1 region
Or
UMN in 2 regions
Or
LMN sign
above UMN signs

Clinically
Possible ALS

UMN + LMN
in 1 region
Or
UMN ≥ 1 region
Plus
EMG
denervation
 ≥ 2 limbs

Clinically
Probable ALS
(Laboratory
supported)

UMN + LMN
in 2 regions

Clinically
Probable
ALS

UMN + LMN
in 3 regions

Clinically
Definite
ALS

B

Awaji- Shima criteria

UMN + LMN
in 1 region
Or
UMN in 2 regions
Or
LMN sign
above UMN signs

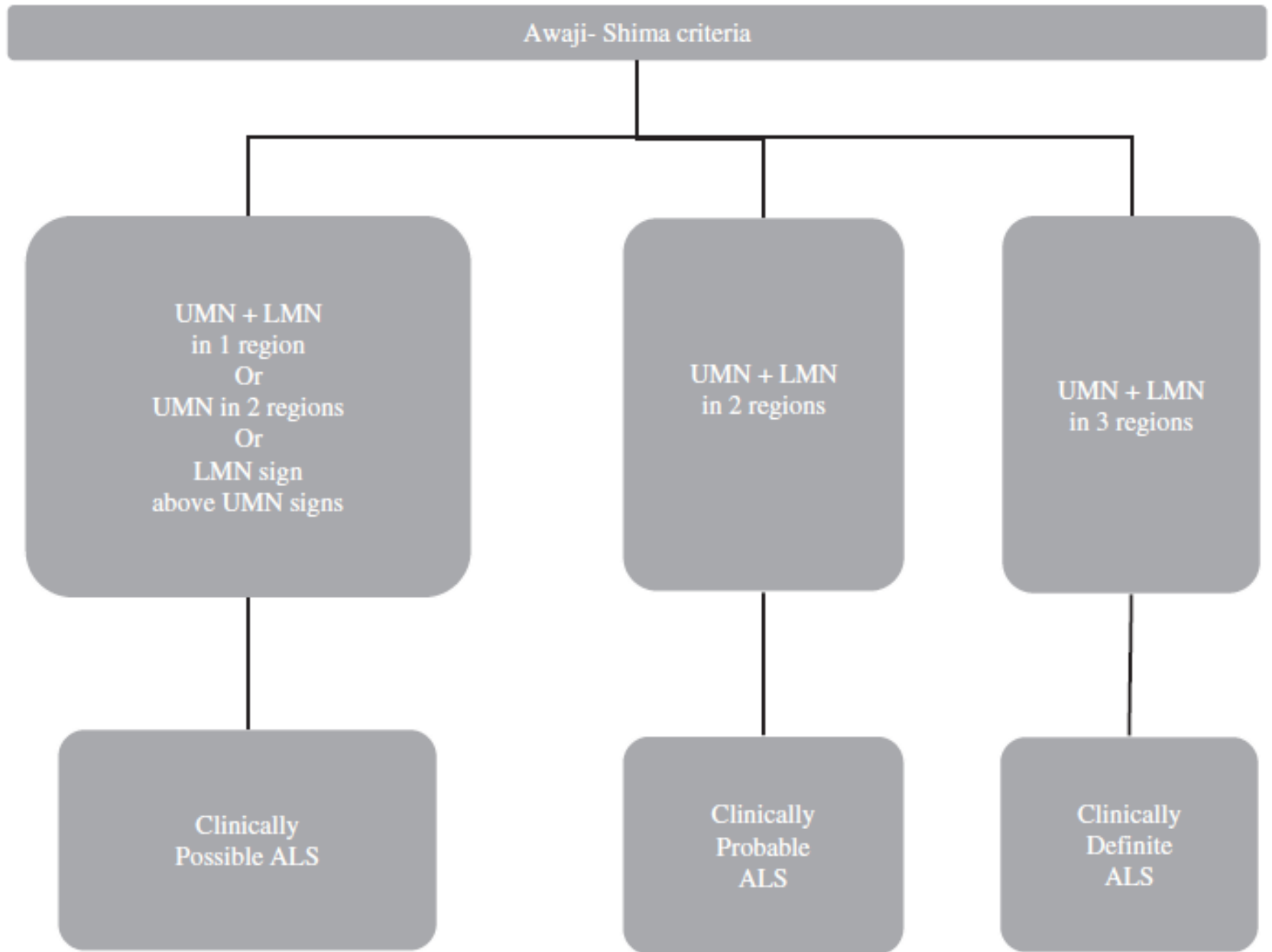
Clinically
Possible ALS

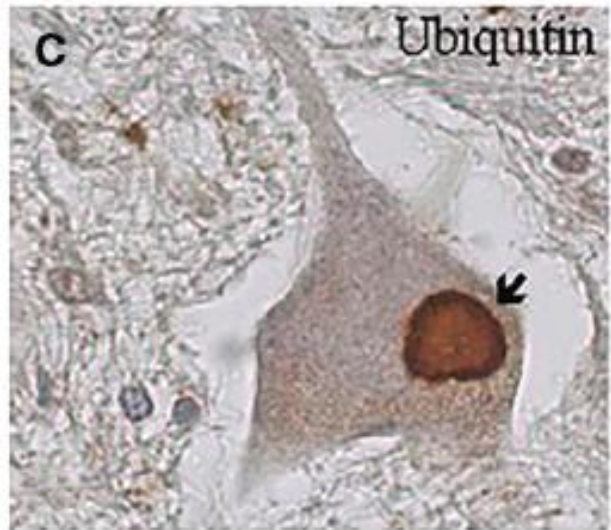
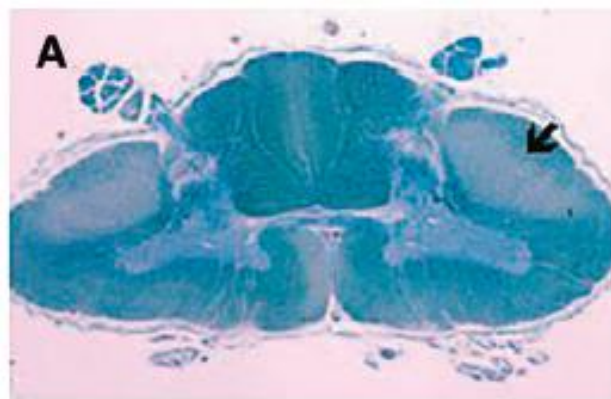
UMN + LMN
in 2 regions

Clinically
Probable
ALS

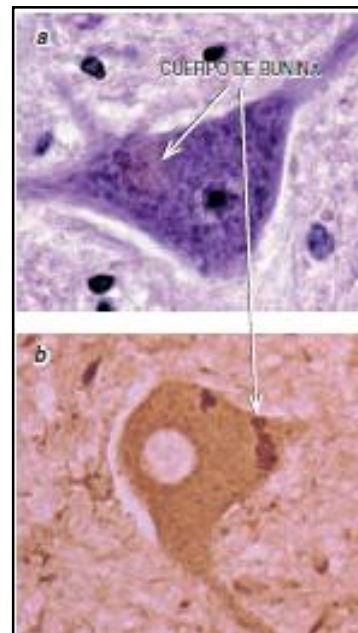
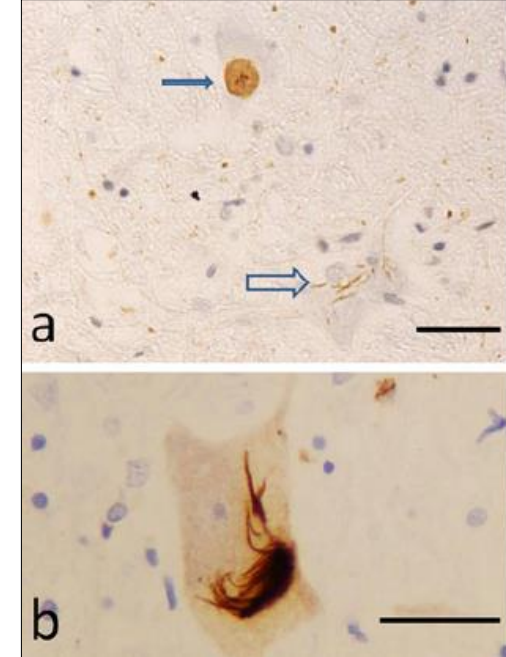
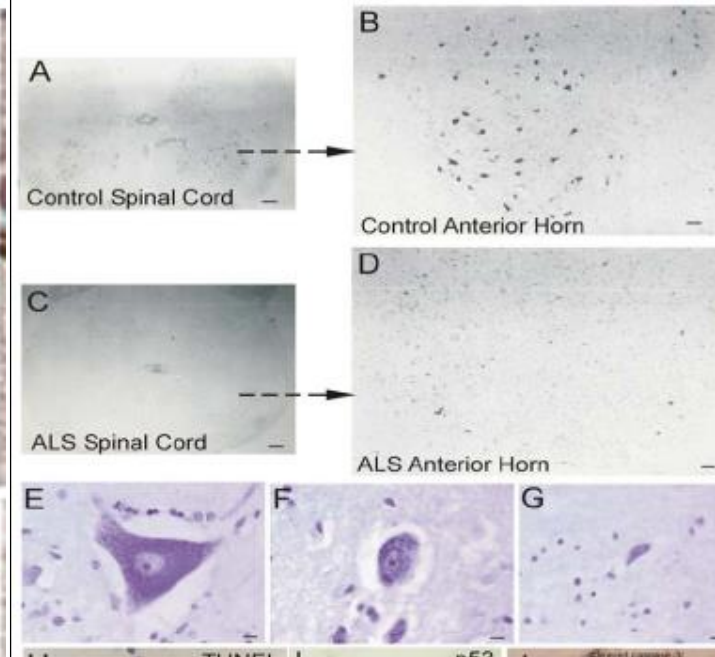
UMN + LMN
in 3 regions

Clinically
Definite
ALS



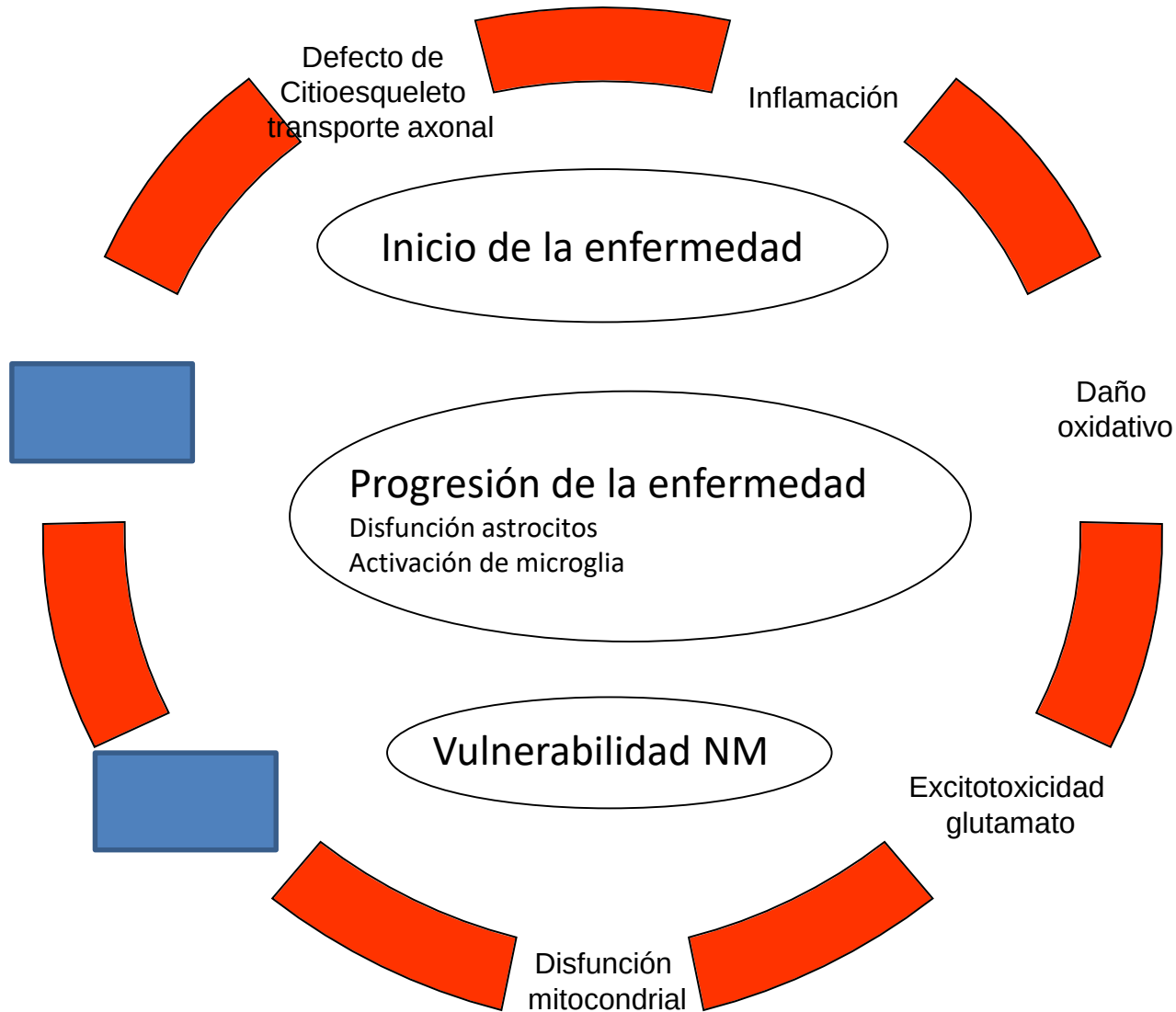


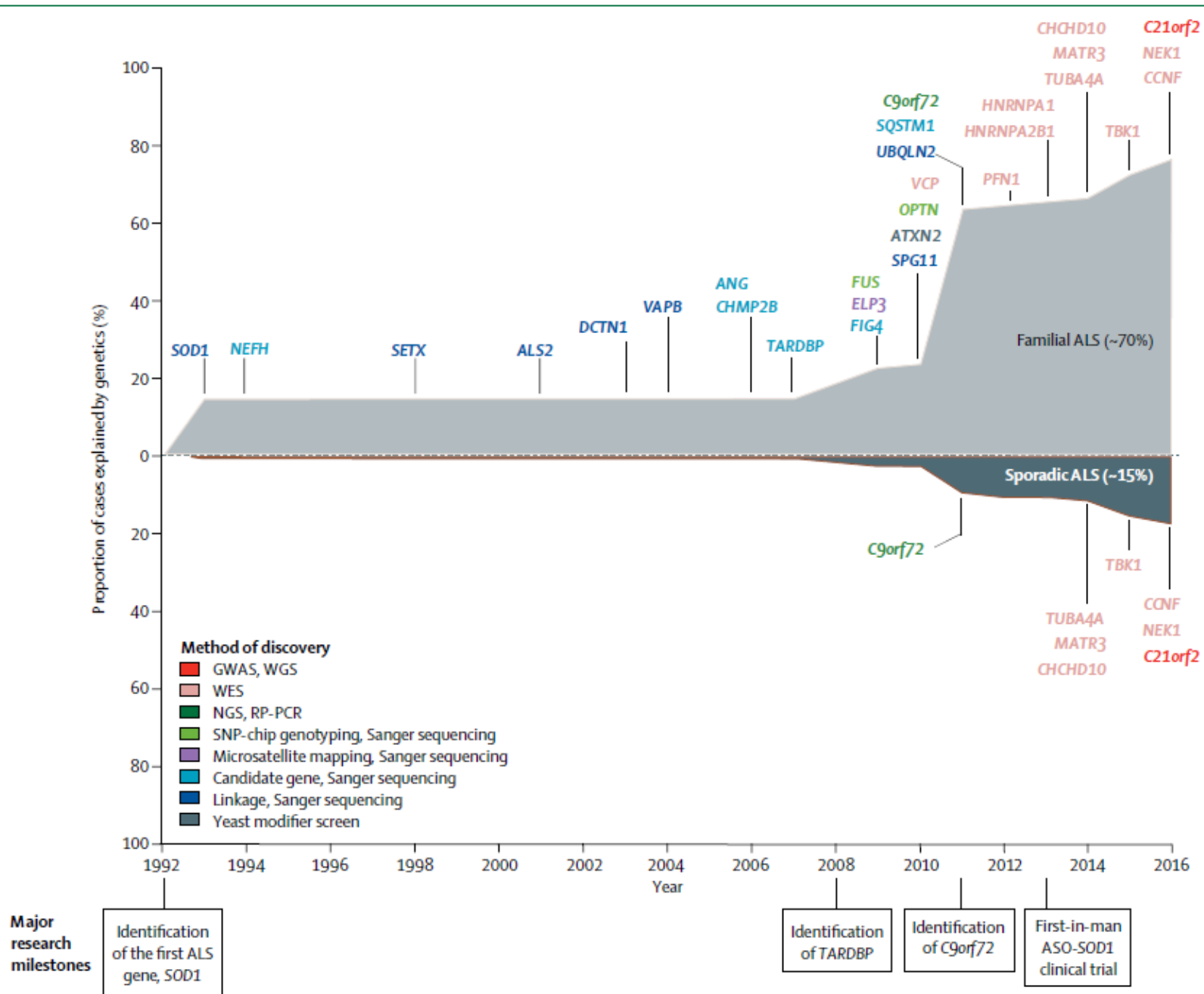
Continuum (Minneapolis Minn) 2014;20(5):1185-1207.



- Pérdida de NMS y NMI
- Degeneración de la vía corticoespinal.
- Presencia de cuerpos de Bunina (70-100%) inclusiones pequeñas eosinófilas hialinas intracitoplasmáticas que tiñen para cistatina y transferrina.
- Inclusiones intraneuronales ubiquitin+ (madejas, esferas) que representan el acumulo anormal de proteínas insolubles, no degradadas por el proteosoma

PATOGENIA DE LA ELA





Genome-wide Analyses Identify KIF5A as a Novel ALS Gene

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Nicolas et al., 2018, Neuron 97, 1268–1283
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CellPress

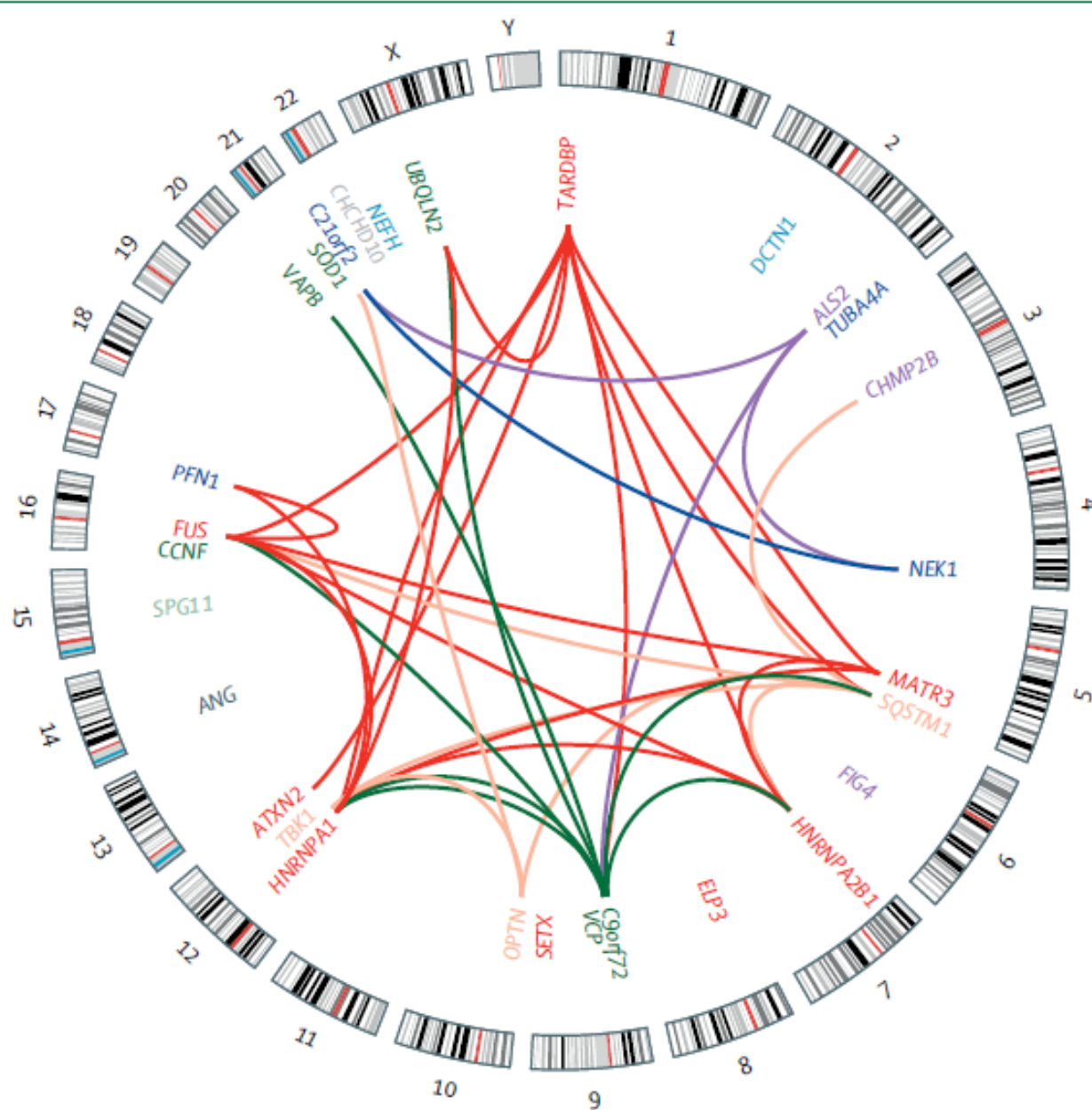
SUMMARY

To identify novel genes associated with ALS, we undertook two lines of investigation. We carried out a genome-wide association study comparing 20,806 ALS cases and 59,804 controls. Independently, we performed a rare variant burden analysis comparing 1,138 index familial ALS cases and 19,494 controls. Through both approaches, we identified *kinesin family member 5A (KIF5A)* as a novel gene associated with ALS. Interestingly, mutations predominantly in the N-terminal motor domain of KIF5A are causative for two neurodegenerative diseases: hereditary spastic paraplegia (SPG10) and Charcot-Marie-Tooth type 2 (CMT2). In contrast, ALS-associated mutations are primarily located at the C-terminal

Analysis of the *C9orf72* Gene in Patients with Amyotrophic Lateral Sclerosis in Spain and Different Populations Worldwide

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ABSTRACT: A hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*) can cause amyotrophic lateral sclerosis (ALS) and/or frontotemporal dementia (FTD). We assessed its frequency in 781 sporadic ALS (sALS) and 155 familial ALS (fALS) cases, and in 248 Spanish controls. We tested the presence of the reported founder haplotype among mutation carriers and in 171 Ceph Europeans from Utah (CEU), 170 Yoruba Africans, 81 Han Chinese, and 85 Japanese subjects. The *C9orf72* expansion was present in 27.1% of fALS and 3.2% of sALS. Mutation carriers showed lower age at



Biological processes implicated in amyotrophic lateral sclerosis

- | | | |
|---|---|---|
| ■ Proteostasis | ■ Cytoskeletal organisation | ■ DNA damage |
| ■ Ribostasis | ■ Axonal transport | ■ Mitochondria function |
| ■ Autophagy | ■ Vesicular trafficking | ■ Angiogenesis |

	Gene	Loci	Genetic effect	Familial amyotrophic lateral sclerosis (%) ^a	Sporadic amyotrophic lateral sclerosis (%) ^a	Implicated amyotrophic lateral sclerosis pathway	Disease features [†]	Other associated allelic disorders	DNA, RNA, and proteins found to interact with target gene [‡]
(Continued from previous page)									
2010	VCP	9p13	Autosomal dominant, de novo	1	1	Proteostasis	Typical amyotrophic lateral sclerosis; frontotemporal dementia	Charcot-Marie-Tooth disease type 2Y; inclusion body myopathy with early-onset Paget disease and frontotemporal dementia 1	FUS, TARDBP, VAPB, HNRNPA1
2006	ANG	14q11	Risk factor	NA	NA	Angiogenesis	Typical amyotrophic lateral sclerosis; frontotemporal dementia	None	None
2009	ELP3	8p21	Undefined	NA	NA	Ribostasis; cytoskeletal integrity	Typical amyotrophic lateral sclerosis	None	None
2009	FUS	16p11	Autosomal dominant, autosomal recessive, de novo	4	1	Ribostasis	Juvenile and adult onset typical or atypical amyotrophic lateral sclerosis; frontotemporal dementia; dementia	Hereditary essential tremor-4	MATR3, TARDBP, TAF15, SMN, VCP, SQSTM1, PFN1
2008	TARDBP	1p36	Autosomal dominant, autosomal recessive, de novo	4	1	Ribostasis	Typical amyotrophic lateral sclerosis; frontotemporal dementia	None	ATXN2, MATR3, UBQLN2, HNRNPA1, HNRNPA1, SQSTM1, UBQLN2, VCP, FUS
2006	CHMP2B	3p11	Autosomal dominant	NA	NA	Vesicular trafficking; proteostasis	Typical amyotrophic lateral sclerosis	Frontotemporal dementia	None
2004	VAPB	20q13	Autosomal dominant	NA	NA	Proteostasis	Typical or atypical amyotrophic lateral sclerosis	Finkel type spinal muscular atrophy	VCP
2003	DCTN1	2p13	Autosomal dominant, risk factor	NA	NA	Axonal transport	Slow, progressive juvenile amyotrophic lateral sclerosis	Distal hereditary motor neuropathy type VIIIB; Perry syndrome	None
2001	ALS2S	2q33	Autosomal recessive	NA	NA	Vesicular trafficking	Slow, progressive, infantile and juvenile amyotrophic lateral sclerosis (mainly affecting upper motor neurons)	Juvenile primary lateral sclerosis; infantile hereditary spastic paraplegia	C21orf2, VCP, NEK1
1998	SETX	9q34	Autosomal dominant	NA	NA	Ribostasis	Slow, progressive, juvenile amyotrophic lateral sclerosis	Autosomal recessive spinocerebellar ataxia type 1	None
1994	NEFH	22q12	Autosomal dominant, risk factor	NA	NA	Axonal transport	Typical amyotrophic lateral sclerosis	Axonal Charcot-Marie-Tooth disease type 2CC	None
1993	SOD1	21q22	Autosomal dominant, autosomal recessive, de novo	12	1–2	Proteostasis; oxidative stress	Typical amyotrophic lateral sclerosis; cognitive impairment (very rare)	None	OPTN

	Gene	Loci	Genetic effect	Familial amyotrophic lateral sclerosis (%) ^a	Sporadic amyotrophic lateral sclerosis (%) ^a	Implicated amyotrophic lateral sclerosis pathway	Disease features ^d	Other associated allelic disorders	DNA, RNA, and proteins found to interact with target gene ^g
2016	<i>C21orf2</i>	21q22.3	Autosomal dominant, risk factor	NA	NA	Cytoskeletal organisation	Typical amyotrophic lateral sclerosis; frontotemporal dementia	Down syndrome; spondylometaphyseal dysplasia; retinal degeneration	ALS2, NEK1
2016	<i>CCNF</i>	16p13.3	Autosomal dominant	4	2	Proteostasis	NA	None	None
2016	<i>NEK1</i>	4q33	Autosomal dominant, autosomal recessive	2	2	Cytoskeletal organisation; DNA damage and cell cycle	Typical amyotrophic lateral sclerosis	Short-rib thoracic dysplasia 6 with or without polydactylism; polycystic kidney disease	ALS2, C21orf2
2015	<i>TBK1</i>	12q14.2	Autosomal dominant, de novo	<1	<1	Autophagy; neuroinflammation	Typical amyotrophic lateral sclerosis; frontotemporal dementia	None	OPTN, SQSTM1
2014	<i>CHCHD10</i>	22q11.23	Autosomal dominant	<1	<1	Mitochondrial function; cellular bioenergetics	Typical amyotrophic lateral sclerosis; frontotemporal dementia; ataxia; myopathy	Spinal muscular atrophy (Jokela type); autosomal dominant isolated mitochondrial myopathy	None
2014	<i>MATR3</i>	5q31.2	Autosomal dominant	<1	<1	Ribostasis	Slow, progressive typical or atypical amyotrophic lateral sclerosis; frontotemporal dementia; myopathy	Vocal cord and pharyngeal dysfunction with distal myopathy	HNRNPA2B1, HNRNPA1, TARDBP, FUS
2014	<i>TUBA4A</i>	2q35	Autosomal dominant	<1	<1	Cytoskeletal organisation; axonal transport	Typical amyotrophic lateral sclerosis; frontotemporal dementia	None	None
2013	<i>HNRNPA1</i>	12q13	Autosomal dominant, de novo, risk factor	NA	NA	Ribostasis	Typical amyotrophic lateral sclerosis; myopathy; cognitive impairment	Inclusion body myositis with early-onset Paget disease without frontotemporal dementia 3; multisystem proteinopathy	HNRNPA2B1, TARDBP, UBQLN2, MATR3, FUS, PPN1
2013	<i>HNRNPA2B1</i>	7p15	Autosomal dominant, risk factor	NA	NA	Ribostasis	Typical amyotrophic lateral sclerosis; myopathy; cognitive impairment	Inclusion body myositis with early-onset Paget disease with or without frontotemporal dementia 2; multisystem proteinopathy	HNRNPA1, TARDBP, FUS, MATR3, SQSTM1
2012	<i>PPN1</i>	17p13	Autosomal dominant	<1	<1	Cytoskeletal organisation; axonal growth and transport	Typical amyotrophic lateral sclerosis	None	FUS, HNRNPA
2011	<i>C9orf72</i>	9p21	Autosomal dominant	40	7	Intracellular trafficking; autophagy; proteostasis; global RNA alterations; nucleocytoplasmic transport	Typical amyotrophic lateral sclerosis; frontotemporal dementia	None	HNRNPA1, HNRNPA2B1, UBQLN2, SQSTM1
2011	<i>SQSTM1</i>	5q35	Autosomal dominant	1	<1	Autophagy; neuroinflammation	Typical amyotrophic lateral sclerosis	Frontotemporal dementia; amyotrophic lateral sclerosis; distal myopathy; childhood-onset neurodegeneration with ataxia, dystonia, and gaze palsy; Paget disease of bone-3	TBK1, TARDBP, OPTN, CHMP2B, FUS, HNRNPA2B1, NEFM
2011	<i>UBQLN2</i>	Xp11	X-linked autosomal dominant	<1	<1	Proteostasis	Typical juvenile or adult onset amyotrophic lateral sclerosis	None	HNRNPA1, TARDBP
2010	<i>ATXN2</i>	12q24	Autosomal dominant, risk factor			Ribostasis	Typical amyotrophic lateral sclerosis	Spinocerebellar ataxia type 2	TARDBP
2010	<i>OPTN</i>	10p13	Autosomal dominant, autosomal recessive	<1	<1	Autophagy; neuroinflammation	Slow, progressive atypical amyotrophic lateral sclerosis	Adult-onset primary open angle glaucoma	TBK1, SQSTM1, SOD1
2010	<i>SPG11S</i>	15q14	Autosomal recessive	NA	NA	DNA damage	Slow, progressive juvenile amyotrophic lateral sclerosis, mainly affecting upper motor neurons	Hereditary spastic paraplegia; Charcot-Marie-Tooth disease, axonal, type 2X; spastic paraplegia type 11	None

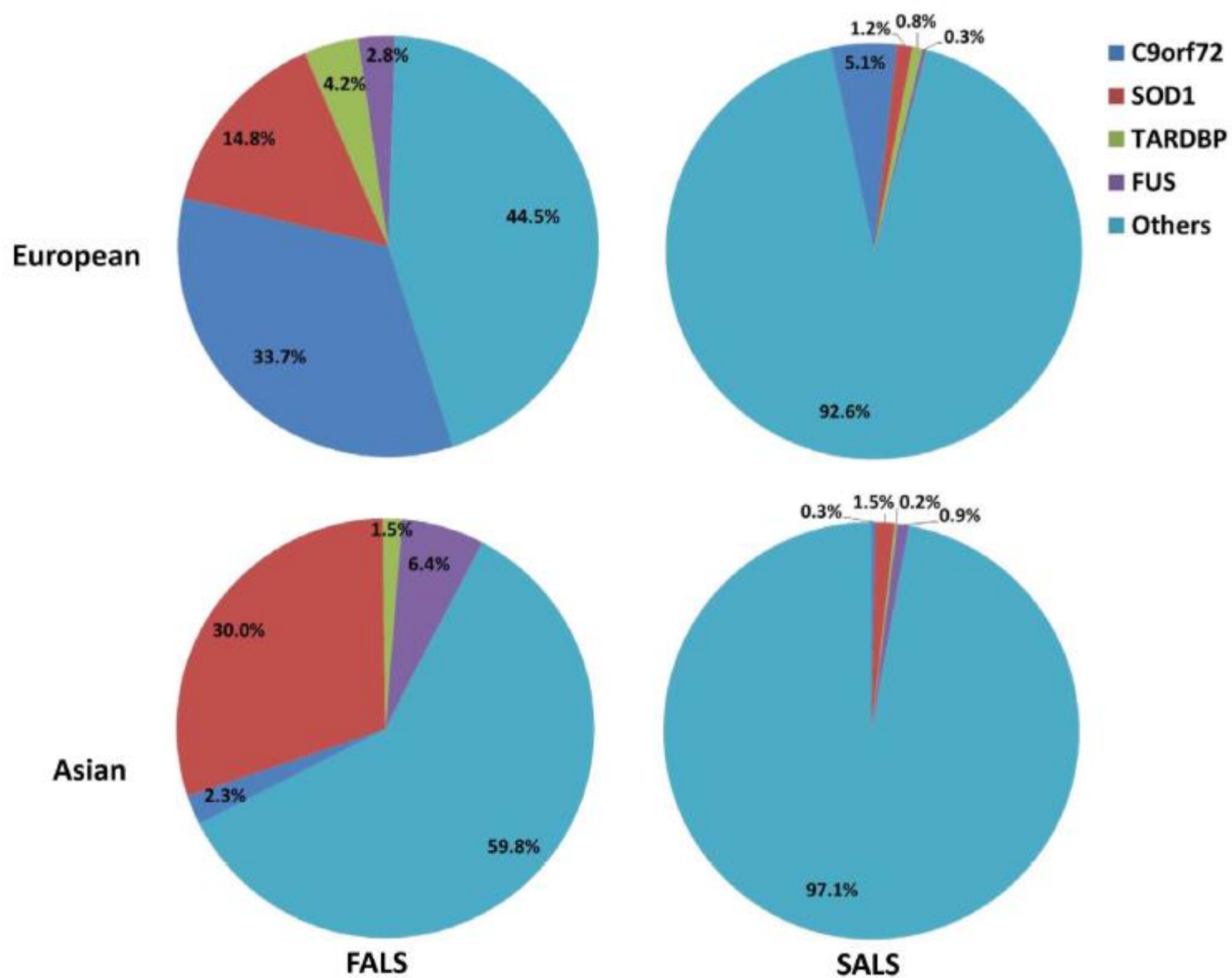
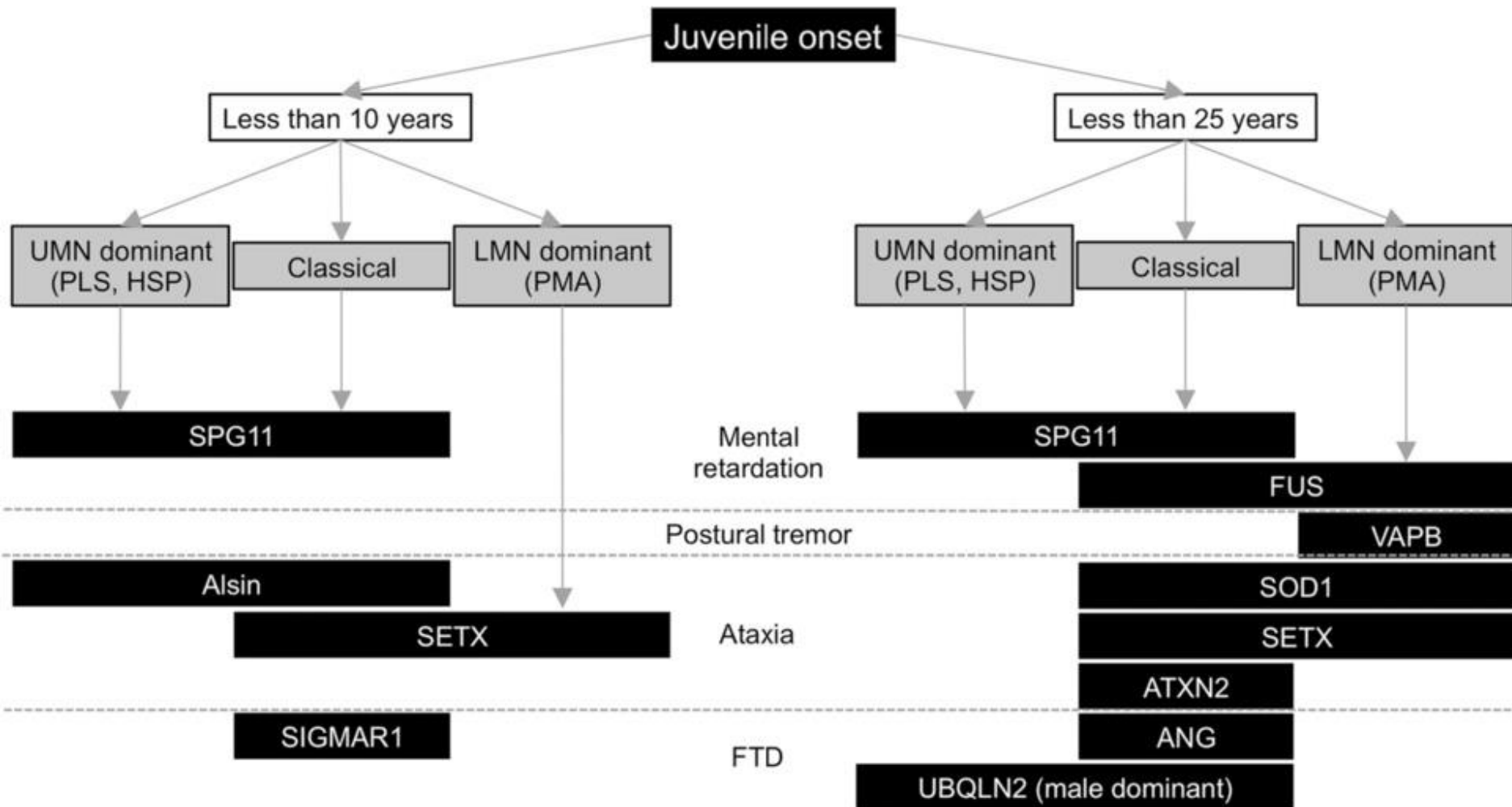


Figure 5 Genetic architecture of FALS and SALS in European and Asian populations. FALS, familial amyotrophic lateral sclerosis; SALS, sporadic amyotrophic lateral sclerosis.



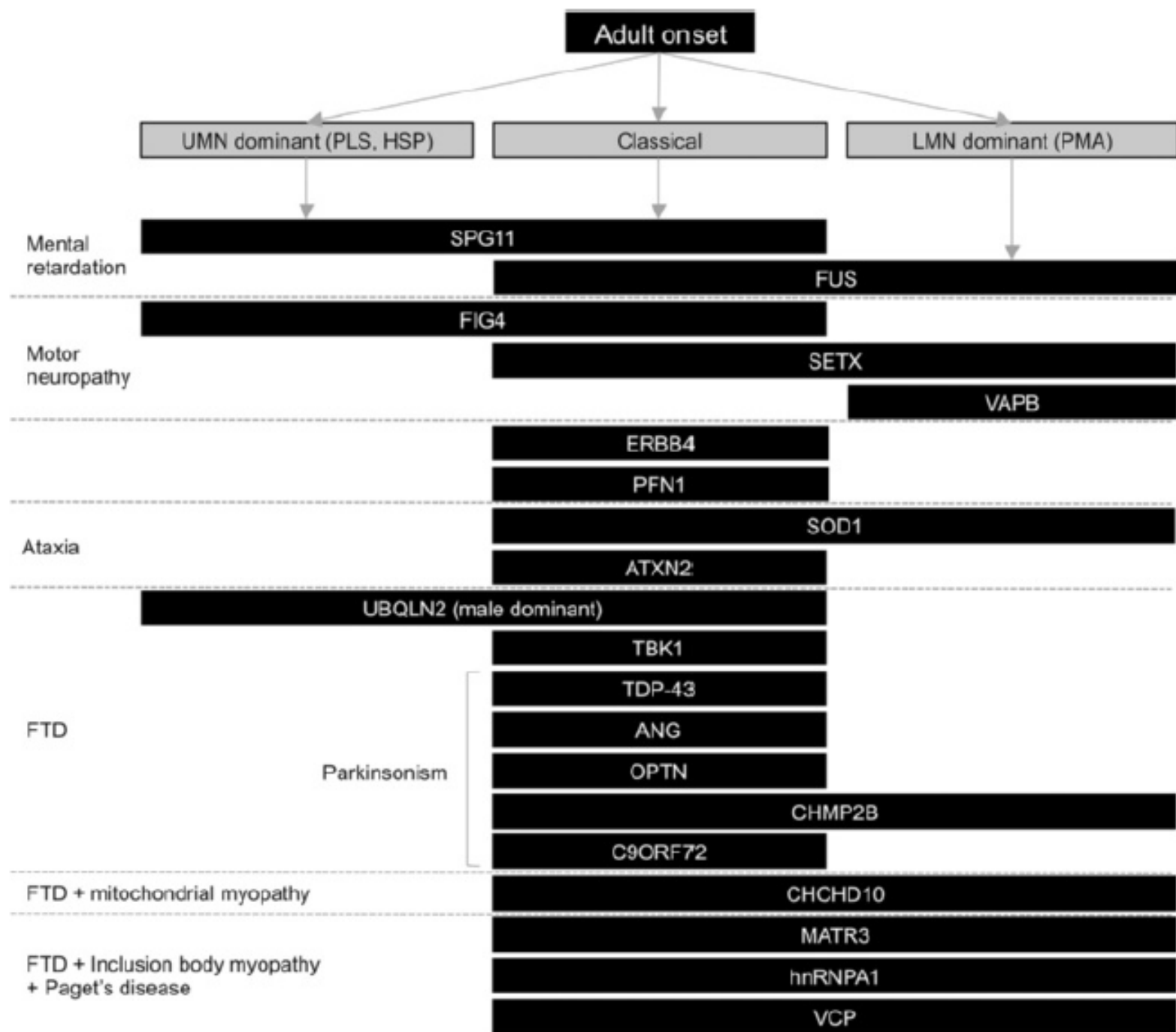


Table I. Clinical characteristics and genetic analysis results of sporadic juvenile ALS patients in our cohort.

No.	Gender	AOO (y)	SOO	Phenotype	Dementia	Survival (m)	Mutated gene	Mutation	De novo mutation
1	F	21	Upper limbs	UMN + LMN	No	41	-	-	-
2	F	23	Lower limbs	LMN	No	>51 (alive)	-	-	-
3	M	24	Upper limbs	UMN + LMN	No	>43 (alive)	-	-	-
4	F	24	Bulbar	UMN + LMN	No	47	-	-	-
5	M	22	Bulbar	UMN + LMN	No	53	-	-	-
6	M	23	Lower limbs	LMN	No	>75 (alive)	-	-	-
7	M	17	Upper limbs	UMN + LMN	No	>61 (alive)	-	-	-
8	F	18	Upper limbs	UMN + LMN	Learning difficulties	25	FUS	p.G504Wfs*12	de novo
9	M	18	Upper limbs	UMN + LMN		>47 (alive)	-	-	-
10	M	24	Upper limbs	LMN		>72 (alive)	-	-	-
11	F	19	Upper limbs	UMN + LMN	No	25	FUS	p.P525L	de novo
12	F	22	Lower limbs	UMN + LMN	No	34	SOD1	p.L84F	NT
13	M	22	Lower limbs	UMN + LMN	No	17	FUS	p.R495X	NT
14	M	24	Upper limbs	LMN	No	>60 (alive)	-	-	-
15	M	13	Lower limbs	UMN + LMN	No	23	FUS	p.P525L	NT
16	M	24	Upper limbs	UMN + LMN	No	63	-	-	-

AOO: age of onset; F: female; LMN: lower motor neuron; M: male; NT: not tested; SOO: site of onset; UMN: upper motor neuron.

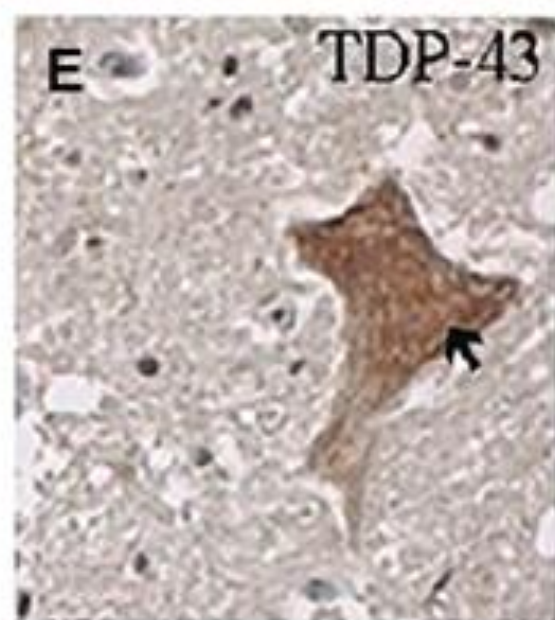
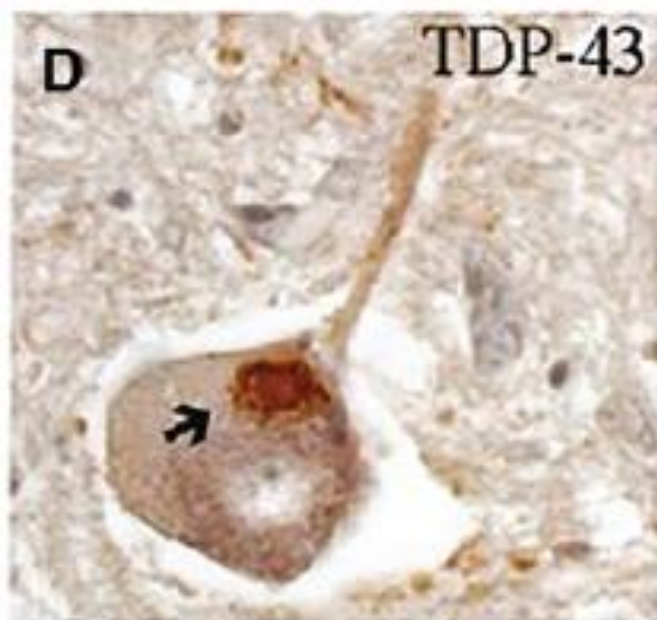
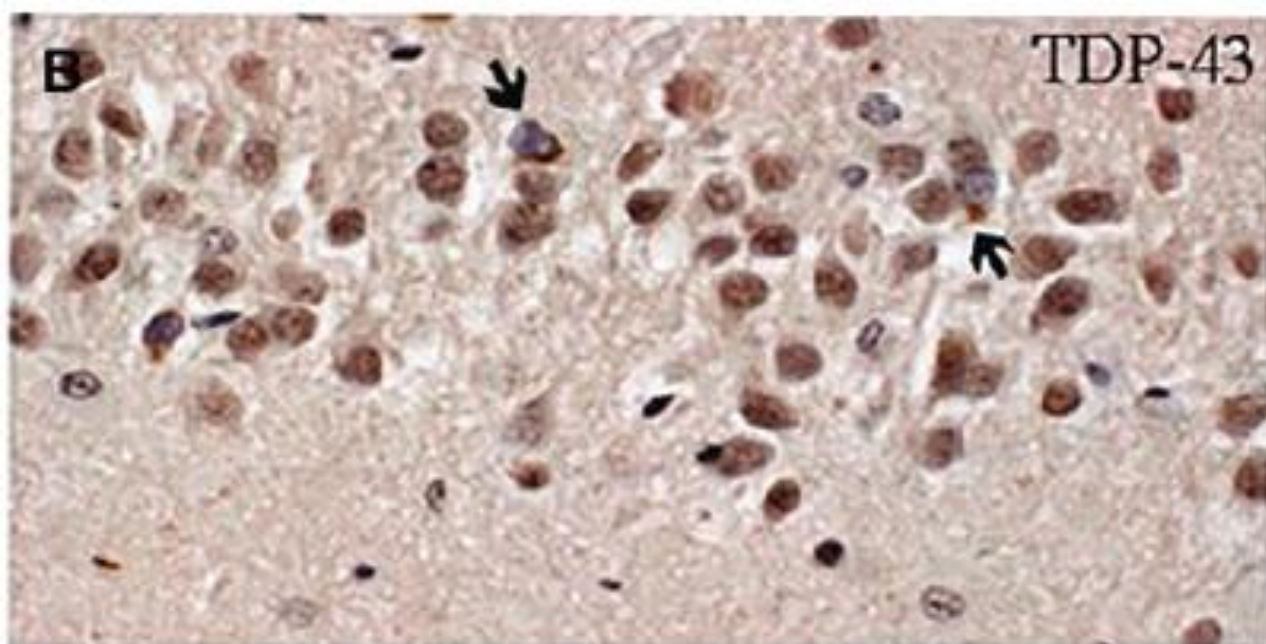
Table II. Summary of juvenile-onset sporadic ALS patients with known mutations in previous studies.

Gene	Amino acid mutation	Gender	Ethnicity	AOO (y)	SOO	Phenotype	Dementia	Disease duration (m)	De novo mutation	Reference
SETX	p.G16S	M	USA	<6	Lower limbs	UMN + LMN	NA	>123(still walk)	NT	Hinano, 2011
SOD1	p.G16S	M	Japanese	18	Upper limbs	UMN + LMN	NA	12*	NT	Kawamata, 1997
	p.P66S	M	Serbian	21	Upper limbs	UMN + LMN	NA	22 (19*)	NT	Keckarevic, 2012
	p.H80A	M	Ireland	24	Lower limbs	LMN + bulbar	NA	18 (9*)	de novo	Alexander, 2002
FUS	p.G466Vfs*14	F	USA	16	Bulbar	LMN + bulbar	No	22(15*)	de novo	DeJesus-Hernandez, 2010
	p.G492EfsX527	M	Japanese	17	Upper limbs + bulbar	UMN + LMN + bulbar	Mental retardation	NA	NT	Yamashita, 2011
	p.D502Tfs*27	M	German	19	Spinal	NA	NA	15 (alive)	de novo	Hübers, 2015
	p.R514S	F	Japanese	23	Upper limbs	UMN + LMN	No	NA	NT	Yamashita, 2011
	p.Q519Ifs*9	M	UK	18	Upper limbs	UMN + LMN + bulbar	Learning difficulties	6	NT	Bäumer, 2010
	p.Q519X	M	French-Canadian	20	Upper limbs	Not reported	NA	12	NT	Belzil, 2011
	p.P525L	F	UK	22	Lower limbs	LMN	No	10	de novo	Bäumer 2010
	p.P525L	F	UK	18	Upper limbs	UMN + LMN	No	11	NT	Bäumer, 2010
	p.P525L	NA	USA	15	NA	Not reported	NA	NA	NT	Brown, 2012
	p.P525L	F	Italian	11	Upper limbs	UMN + LMN	No	14*	de novo	Conte, 2012
	p.P525L	F	USA	12	Upper limbs	LMN	Learning difficulties	20	de novo	Huang, 2010
	p.P525L	F	German	18	Bulbar	NA	NA	9 (alive)	de novo	Hübers, 2015
	p.P525L	M	German	20	Bulbar	NA	NA	15 (alive)	de novo	Hübers, 2015
	p.P525L	M	German	24	Bulbar	NA	NA	7	de novo	Hübers, 2015

AOO: age of onset; F: female; LMN: lower motor neuron; M: male; NA: no data available; NT: not tested; SOO: site of onset; UMN: upper motor neuron. Disease duration was defined as the time from onset of the disease to death/tracheotomy.

*The time from onset to starting tracheotomy.

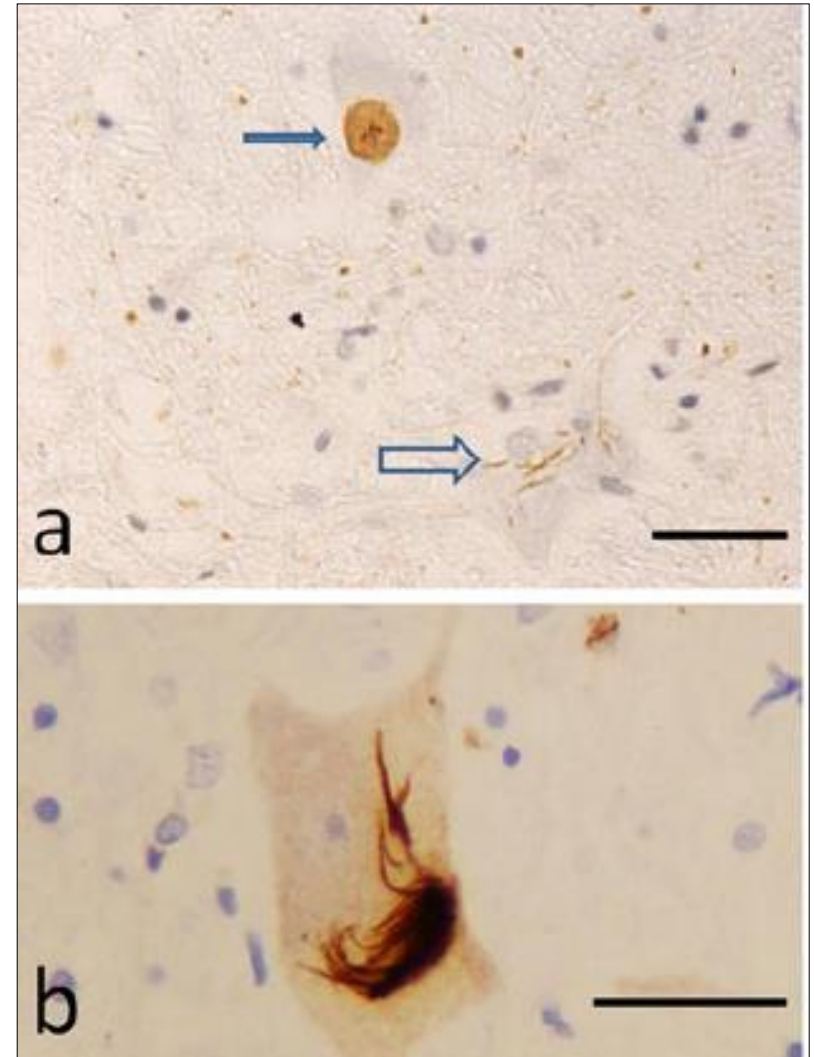
- Base datos 201 ELA
- Inicio 35 años 6 casos
 - 3 M y 3 V (17-34 años)
 - MNS+MNI 5 caso y MNI 1 caso
 - 5 esporádicos 1 familiar (mutación SOD V84F)

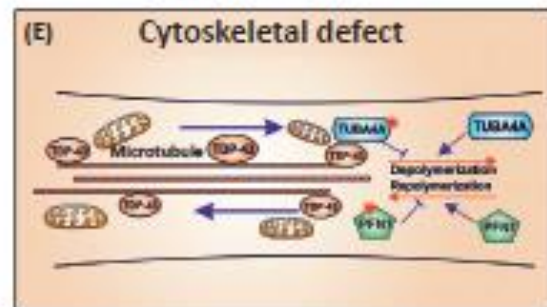
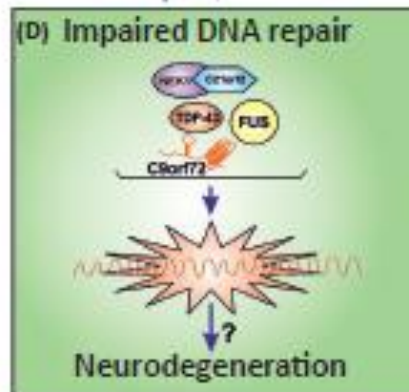
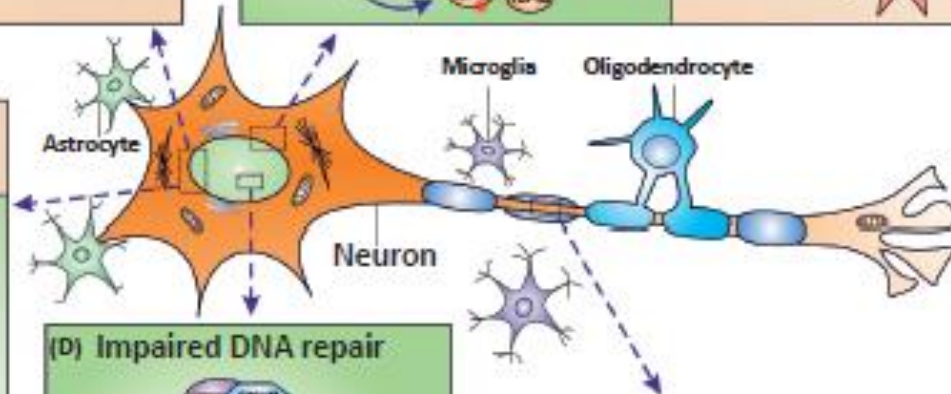
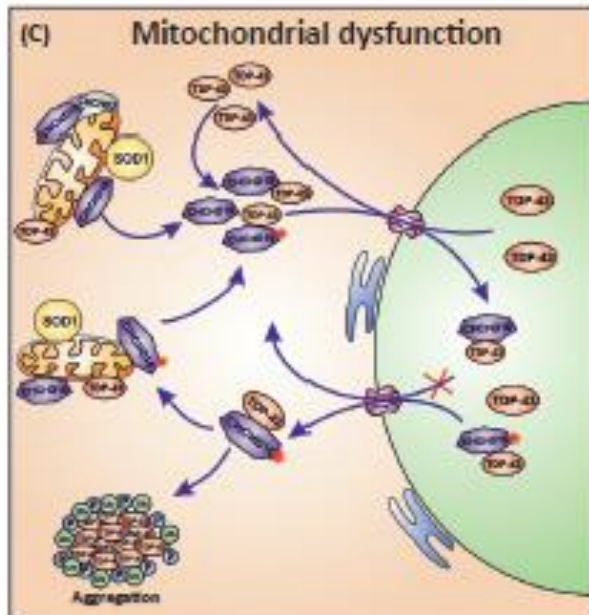
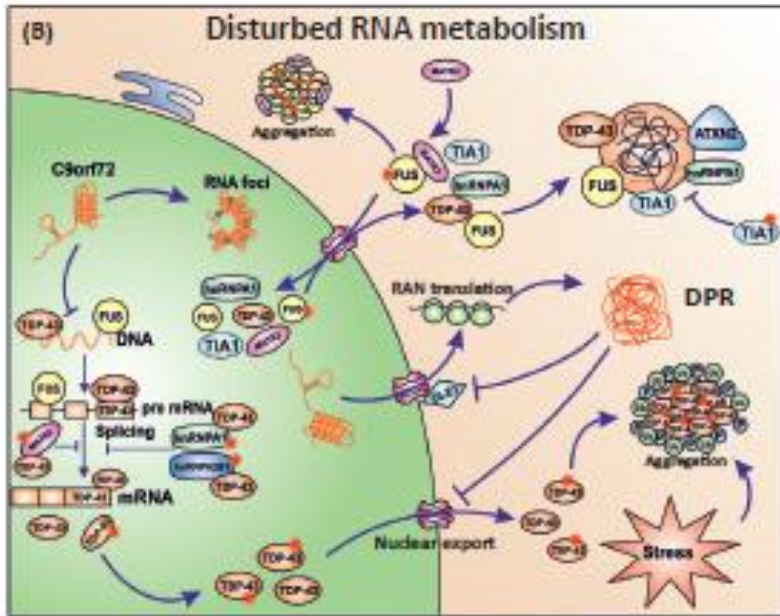
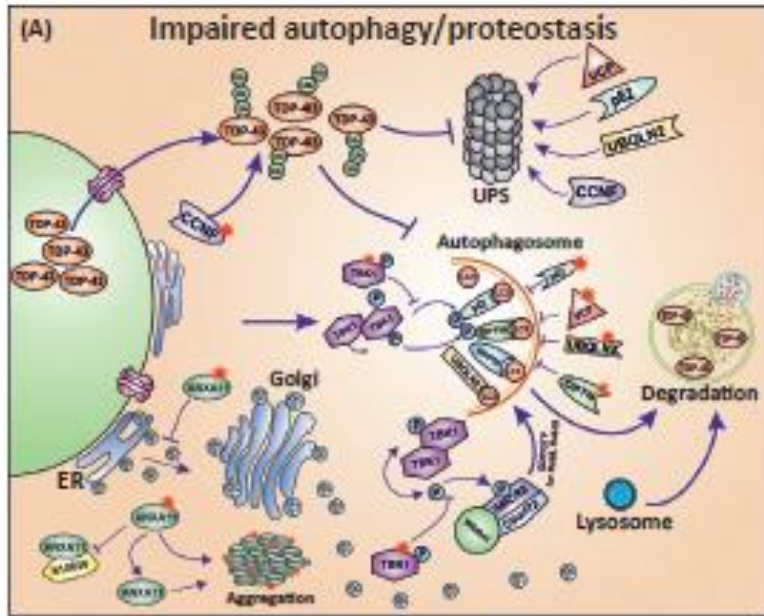


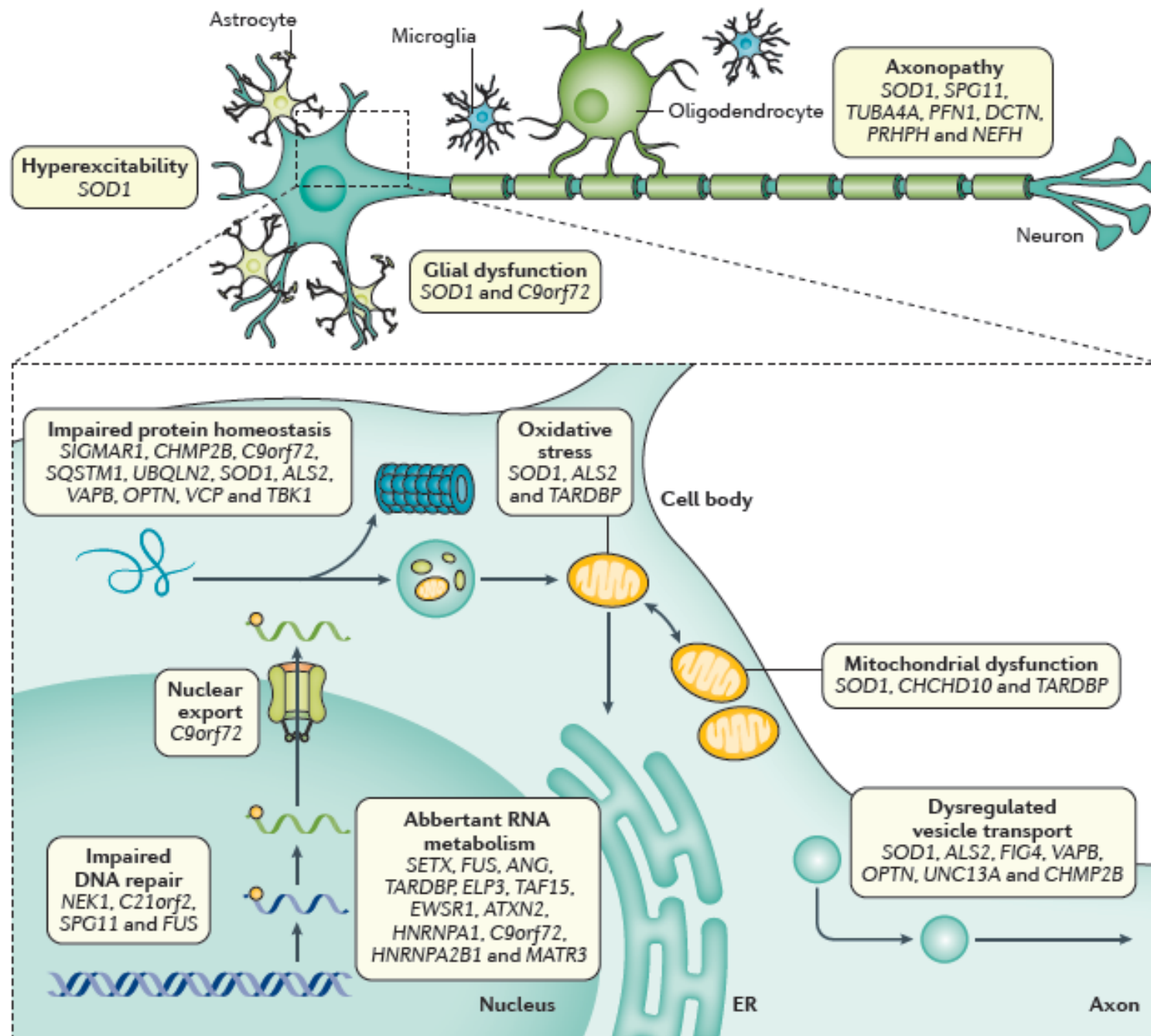
Anatomía Patológica UbiquitinaTDP-43

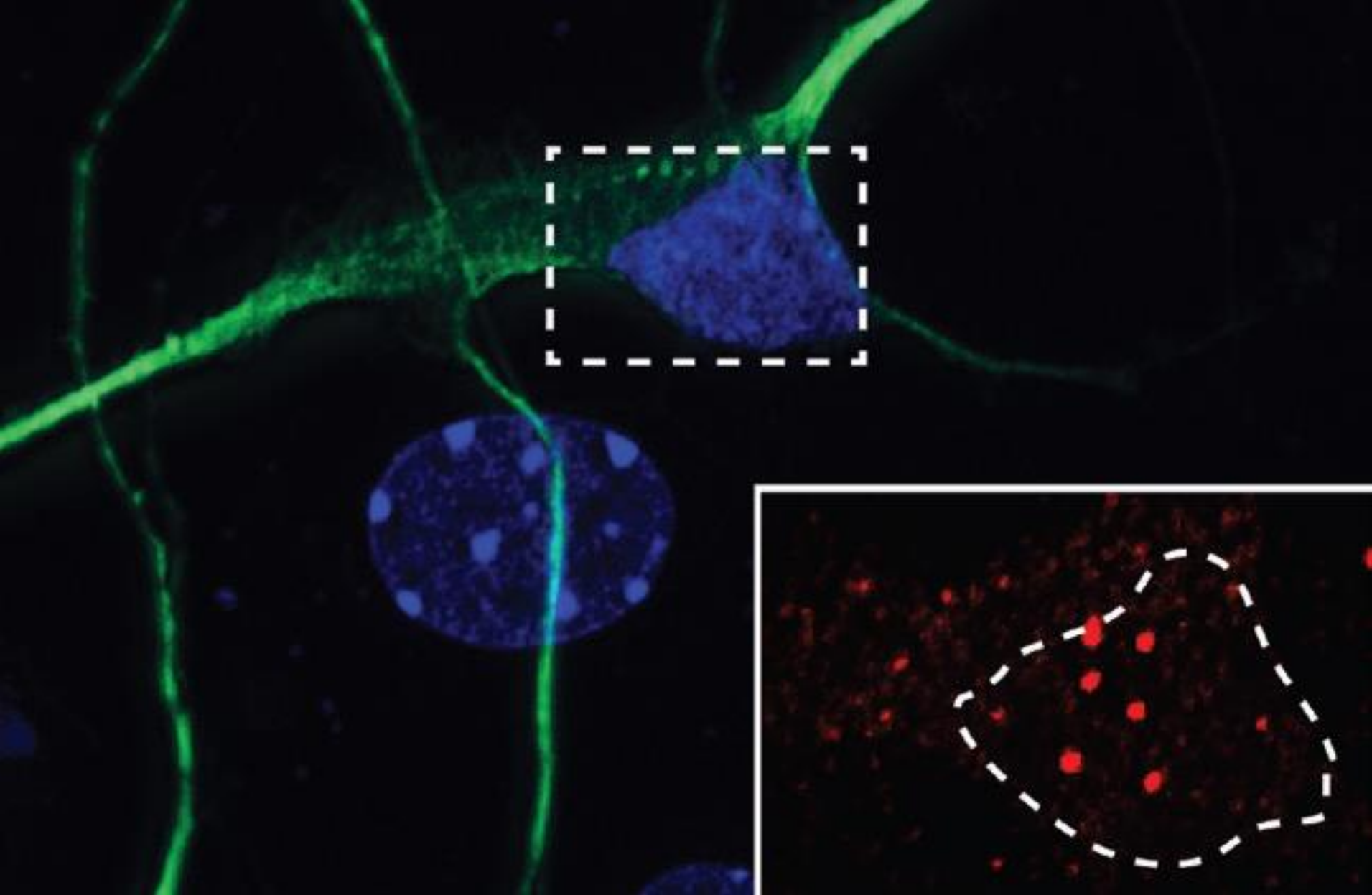
- La proteína transportadora de DNA TAR, TDP-43 es uno de los mayores componentes de esta inclusiones en la ELAE y en DFT (y otras formas de ELAF relacionados con otros genes).
- **La ELA SOD1 tiene inclusiones ubiquitin+ pero TDP-43 -**
- TDP-proteinopatía puede representar una patología final asociada a múltiples genes
- Considerar a la DFT y ELAE el espectro clínico de un mecanismo patogénico común

Clinical and Pathological Relationships Between ALS and FTL-D-U (FTLD-TDP)









C9ORF72 HALLAZGO CARACTERISTICO DE FOCOS DE RNA (ROJO)
VERDE: MAP2 MARCADOR NEURONAL / AZUL: DAP MARCADOR NUCLEAR

A model of ALS progression based on focal onset and spread

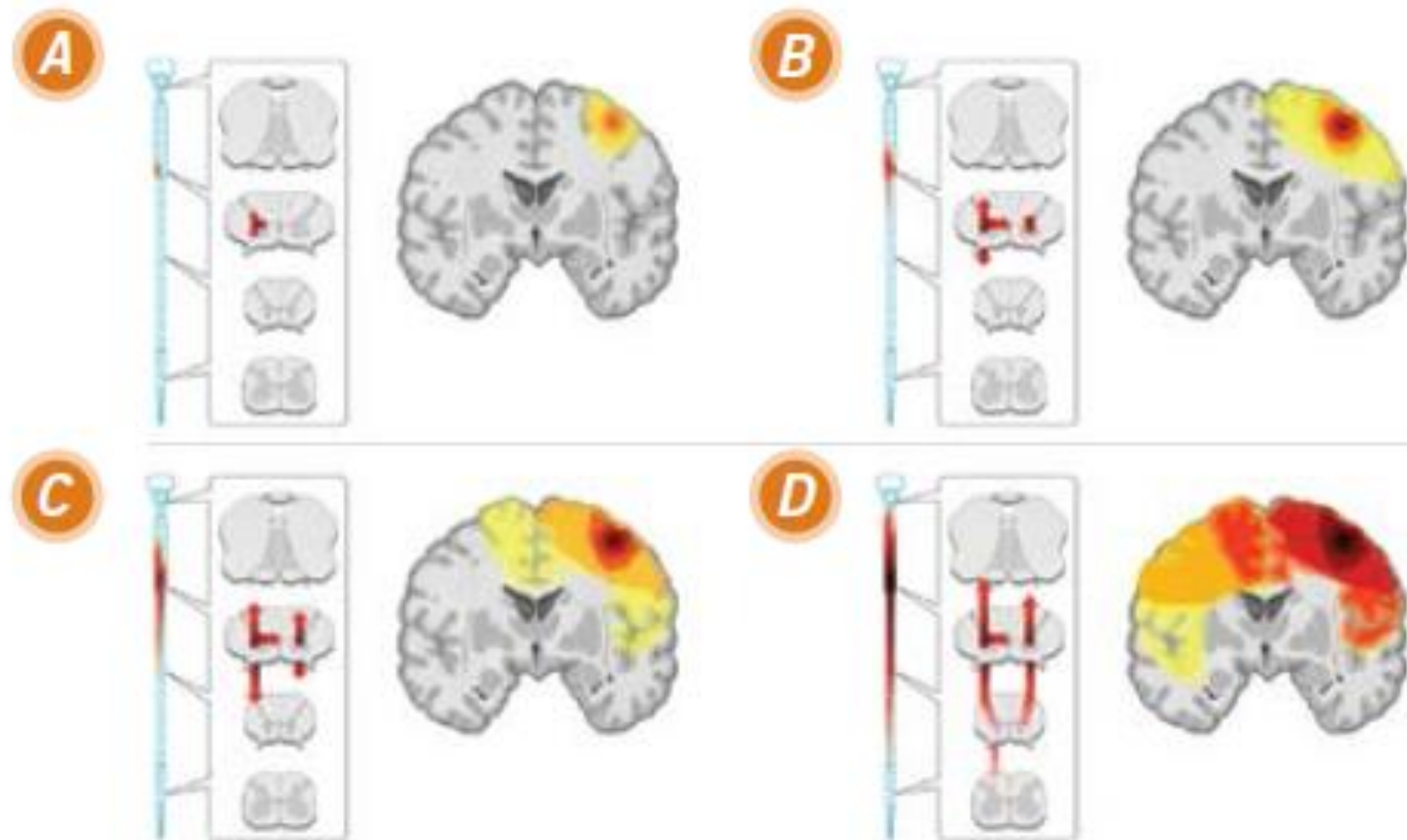
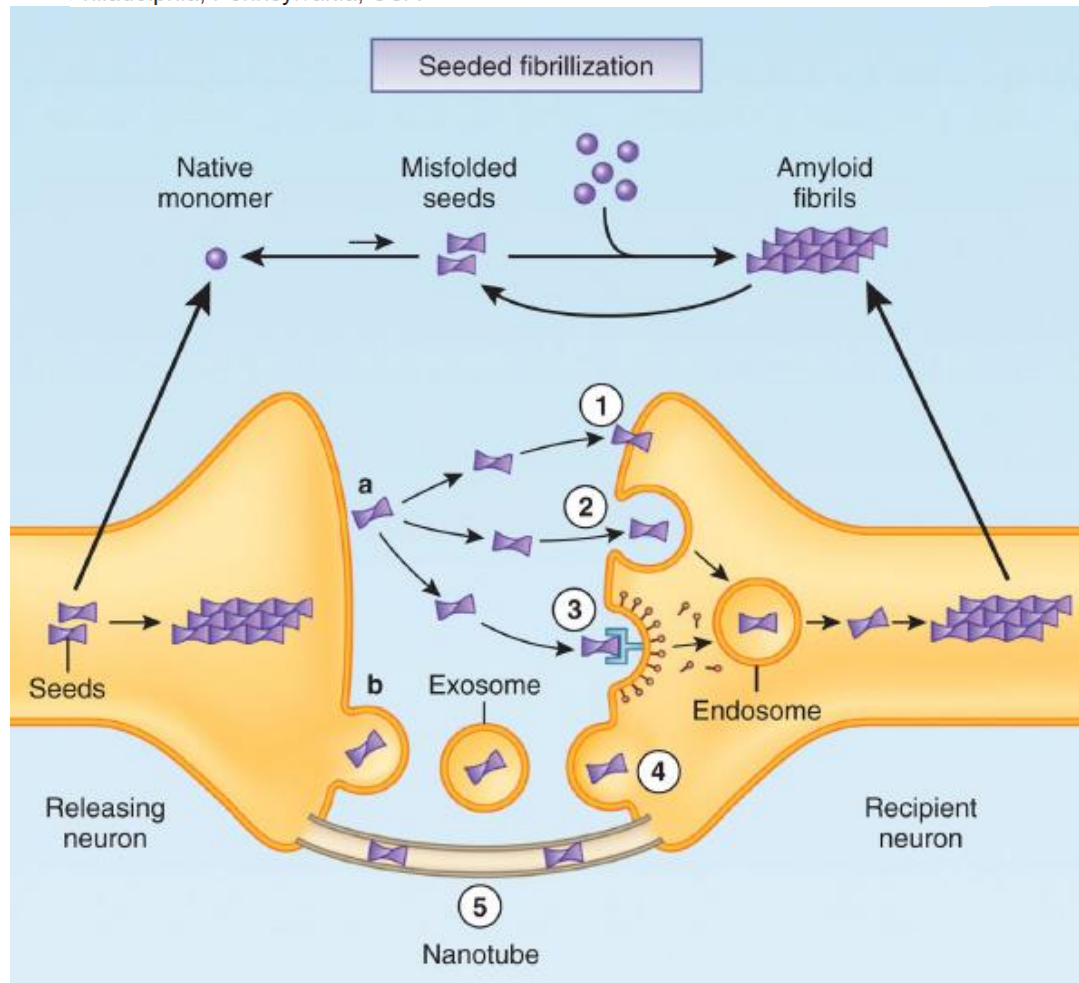


Image courtesy of Ravits, J. M. et al. *Neurology* 2009;73:805-811

Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases

Jing L Guo and Virginia M Y Lee

Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania, USA





Research Report

CSF from amyotrophic lateral sclerosis patients produces glutamate independent death of rat motor brain cortical neurons: Protection by resveratrol but not riluzole

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Antonio Guerrero^c, Antonio G. García^{a,d}

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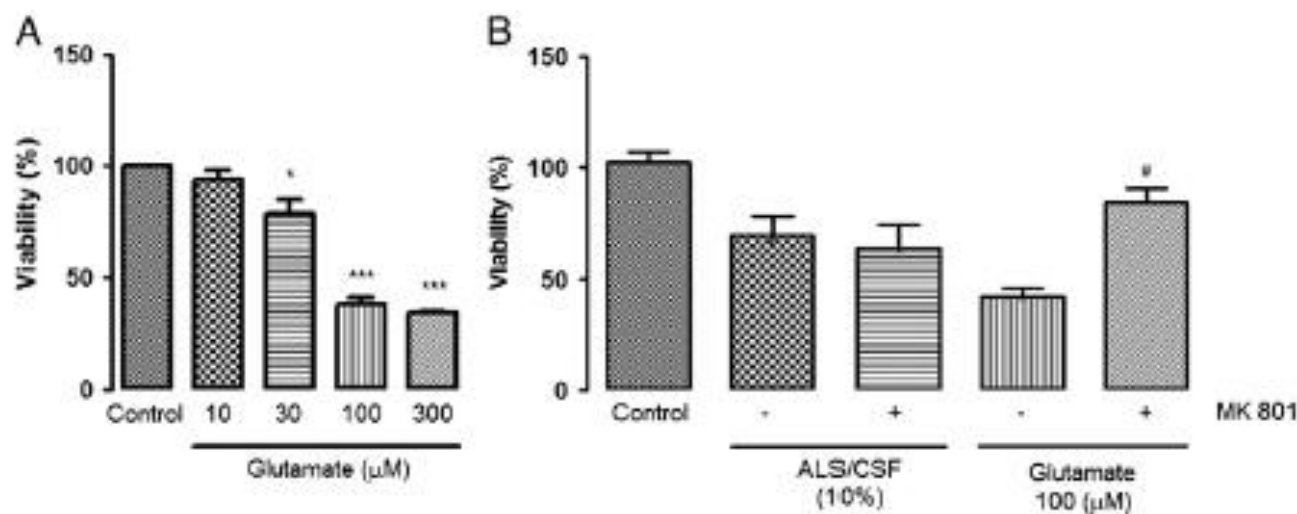


Fig. 3 – Neurotoxic effects of glutamate on cortical motor neurons. Cells were incubated for 24 h with increasing glutamate concentrations from 10 to 300 μM (A) or with 10% ALS/CSF or 100 μM glutamate and with or without 300 nM MK801 (B). Results are expressed as mean ± S.E.M. from at least 5 experiments. **P* < 0.05, ****P* < 0.001 versus the corresponding viability obtained in control group, **P* < 0.05 versus the corresponding viability obtained in neurons without MK801.



REVIEW ARTICLE

Cerebrospinal fluid cytotoxicity in lateral amyotrophic sclerosis

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**Neuro-
degenerative
Diseases**

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Published online: December 20, 2013

The Neuroprotection Exerted by Memantine, Minocycline and Lithium, against Neurotoxicity of CSF from Patients with Amyotrophic Lateral Sclerosis, Is Antagonized by Riluzole

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Lucía Galán^{c,d} Dolores Viña^e Ulises Gómez-Pinedo^d Álvaro Vela^c
Antonio Guerrero^{c,d} Eduardo Martínez-Vila^f Antonio G. García^{a,b}

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ORIGINAL

La infusión intracerebroventricular prolongada de líquido cefalorraquídeo procedente de pacientes con esclerosis lateral amiotrófica provoca cambios histológicos en el cerebro y la médula espinal de la rata similares a los hallados en la enfermedad

U. Gómez-Pinedo^{a,*}, L. Galán^b, M. Yañez^c, J. Matias-Guiu^b, C. Valencia^b,
A. Guerrero-Sola^b, F. Lopez-Sosa^a, J.R. Brin^c, M.S. Benito-Martin^a,
G. Leon-Espinosa^a, A. Vela-Souto^b, C. Lendinez^c, T. Guillamon-Vivancos^a,
J.A. Matias-Guiu^{a,b}, J.A. Arranz-Tagarro^d, J.A. Barcia^c y A.G. Garcia^d

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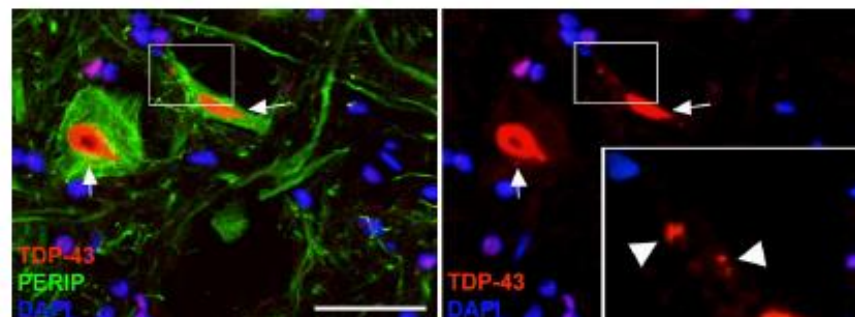


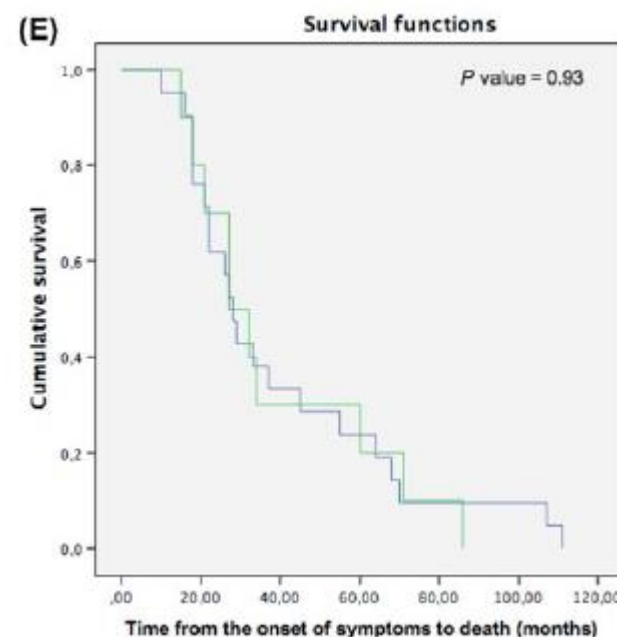
Figura 7 Imágenes en las que se observa que los animales tratados con cELA-LCR mostraron inclusiones citoplasmáticas de TDP-43 en las neuronas de la médula espinal (flechas). En el detalle se observan las inclusiones (cabezas de flecha). Escala: 40 μ m.

Cerebrospinal fluid cytotoxicity does not affect survival in amyotrophic lateral sclerosis

L. Galán¹ | J. Matías-Guiu¹ | J. A. Matías-Guiu¹ | M. Yáñez^{2,3} | V. Pytel¹ |
A. Guerrero-Sola¹ | A. Vela-Souto¹ | J. A. Arranz-Tagarro^{2,3} | U. Gómez-Pinedo¹ |
A. G. García³

TABLE 1 Demographic and clinical characteristics of patients grouped according to the presence of cytotoxicity in the cerebrospinal fluid

	Cytotoxic CSF (n=21)	Non-cytotoxic CSF (n=10)	P-value
Age at diagnosis (years)	59.0±10.4	59.0±9.9	0.84
Sex (female)	47.6% (n=10)	40% (n=4)	0.69
Time from symptom onset to diagnosis (months)	7.4±3.6	13.1±13.2	0.14
Bulbar onset	42.9% (n=9)	30.0% (n=3)	0.49
Gastrostomy	61.9% (n=13)	50% (n=5)	0.10
Respiratory assistance	85.7% (n=18)	70% (n=7)	0.29
Time from diagnosis to gastrostomy (months)	11.6±5.3	7.8±3.9	0.18
Time from diagnosis to respiratory assistance (months)	17.8±17.4	16.7±14.0	0.92
Survival from diagnosis (months)	32.5±26.8	25.8±18.9	0.58
Survival from the onset of symptoms to death (months)	40.2±28.8	39.1±24.4	0.89





RESEARCH ARTICLE

Riluzole does not improve lifespan or motor function in three ALS mouse models

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& JOCHEN H. M. PREHN

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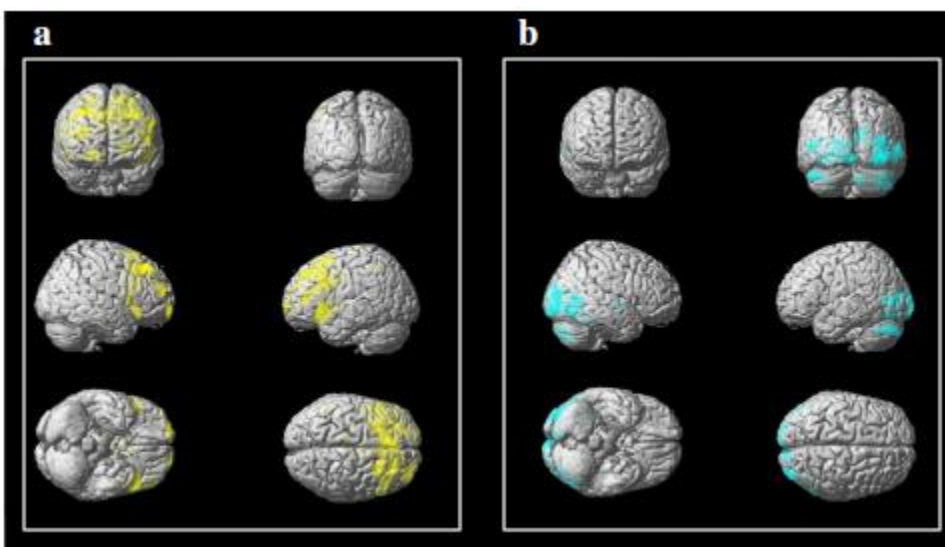
Abstract

Background: Riluzole is the most widespread therapeutic for treatment of the progressive degenerative disease amyotrophic lateral sclerosis (ALS). Riluzole gained FDA approval in 1995 before the development of ALS mouse models. We assessed riluzole in three transgenic ALS mouse models: the SOD1^{G93A} model, the TDP-43^{A315T} model, and the recently developed FUS (1-359) model. **Methods:** Age, sex and litter-matched mice were treated with riluzole (22 mg/kg) in drinking water or vehicle (DMSO) from symptom onset. Lifespan was assessed and motor function tests were carried out twice weekly to determine whether riluzole slowed disease progression. **Results:** Riluzole treatment had no significant benefit on lifespan in any of the ALS mouse models tested. Riluzole had no significant impact on decline in motor performance in the FUS (1-359) and SOD1^{G93A} transgenic mice as assessed by Rotarod and stride length analysis. **Conclusions:** Riluzole is widely prescribed for ALS patients despite questions surrounding its efficacy. Our data suggest that if riluzole was identified as a therapeutic candidate today it would not progress past pre-clinical assessment. This raises questions about the standards used in pre-clinical assessment of therapeutic candidates for the treatment of ALS.

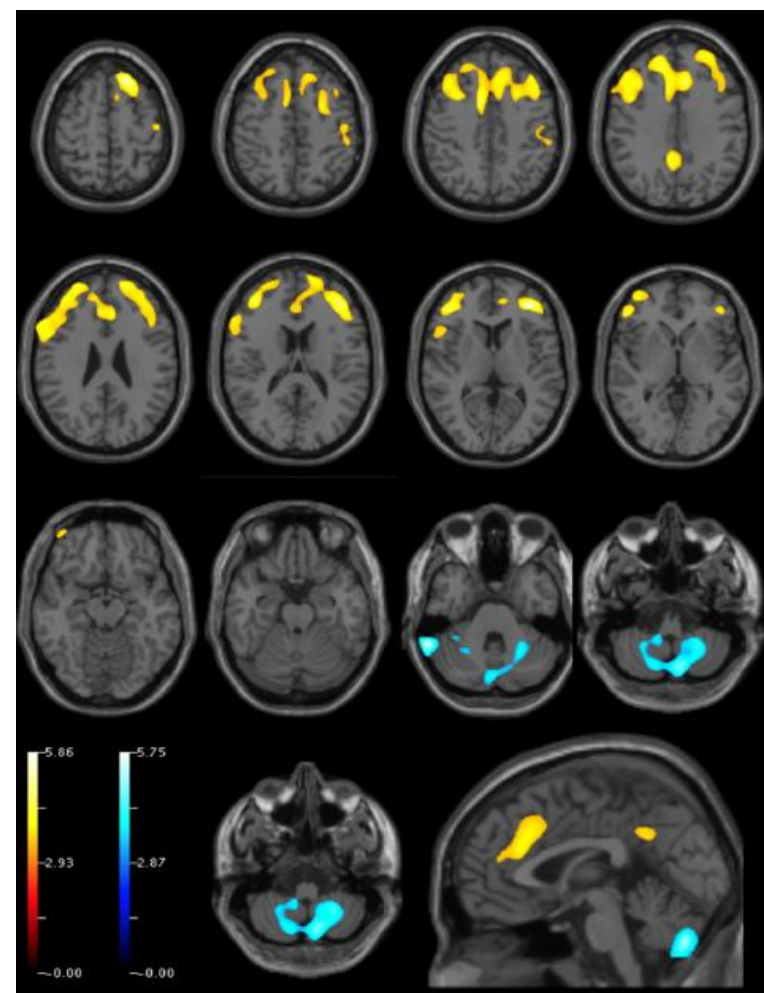
ORIGINAL ARTICLE

Amyloid- and FDG-PET imaging in amyotrophic lateral sclerosis

Jordi A. Matías-Guiu¹ · Vanesa Pytel¹ · María Nieves Cabrera-Martín² · Lucía Galán¹ ·
María Valles-Salgado¹ · Antonio Guerrero¹ · Teresa Moreno-Ramos¹ ·
Jorge Matías-Guiu¹ · José Luis Carreras²



Conclusions We have identified two main patterns of brain metabolism with an association to cognitive status. Only a subgroup of patients showed an increased uptake of the amyloid tracer. Our results suggest that ALS is heterogeneous from a clinical, metabolic, and molecular standpoint.



Immununochemical Markers of the Amyloid Cascade in the Hippocampus in Motor Neuron Diseases

Ulises Gómez-Pinedo¹, Rocio N. Villar-Quiles², Lucia Galán², Jordi A. Matias-Guiu², Maria S. Benito-Martin¹, Antonio Guerrero-Sola², Teresa Moreno-Ramos² and Jorge Matias-Guiu^{1,2*}

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Objective: Considering that dementia is one of the most frequent non-motor symptoms in amyotrophic lateral sclerosis (ALS) and that hippocampus is one of the brain areas with greater presence of amyloid-related changes in neurodegenerative diseases, our aim was to analyze the molecular markers of the amyloid cascade of APP in pathology studies of the hippocampus of autopsied patients with ALS and ALS-frontotemporal dementia (FTD).

Methods: We included nine patients with MND and four controls. Immunohistochemical studies and confocal microscopy were used to analyze the expression of APP, TDP-43, p-h-TDP-43, A β , APP intracellular cytoplasmatic domain (AICD) peptide, Fe65 protein, and p-TAU in the hippocampus of seven patients with ALS, two patients with ALS-FTD, and four controls. These findings were correlated with clinical data.

Results: Patients displayed increased expression of APP and A β peptide. The latter was correlated with cytoplasmic p-h-TDP-43 expression. We also found decreased Fe65 expression. A parallel increase in AICD expression was not found. Patients showed increased expression of p-TAU in the hippocampus. Findings were similar in patients with ALS and those with ALS-FTD, though more marked in the latter group.

Conclusion: Post-mortem analyses showed that the amyloid cascade is activated in the hippocampus of patients with MND and correlated with cytoplasmic p-h-TDP-43 expression. The number of intracellular or extracellular aggregates of A β peptides was not significant.

RESEARCH ARTICLE

Open Access



Amyotrophic lateral sclerosis modifies progenitor neural proliferation in adult classic neurogenic brain niches

Lucía Galán^{1*}, Ulises Gómez-Pinedo², Antonio Guerrero¹, Jose Manuel García-Verdugo³ and Jorge Matías-Guiu²

Methods: We studied 9 autopsies of patients with ALS (including 2 with ALS-FTD) and 4 controls. ALS was confirmed histologically. Studies of the SVZ and SGZ were conducted using markers of proliferation (Ki-67, PCNA), of pluripotent neural progenitor cells (GFAP δ), neuroblasts (PSA-NCAM, DCX, TUJ1), and an astrocyte marker (GFAP). Results were analyzed with non-parametric tests. We then studied correlations between the different markers and the percentage of phosphorylated TDP-43 (pTDP-43).

Results: We observed a statistically significant increase in proliferation in the SVZ in all patients with ALS. While this increase was more marked in ALS forms associated with dementia, the small sample size does not permit a statistical subgroup analysis. In contrast, proliferation in the SGZ was decreased in all patients. These alterations showed a positive and direct correlation with the percentage of pTDP-43 in the SVZ, and a negative, exponential correlation with that percentage in the SGZ.

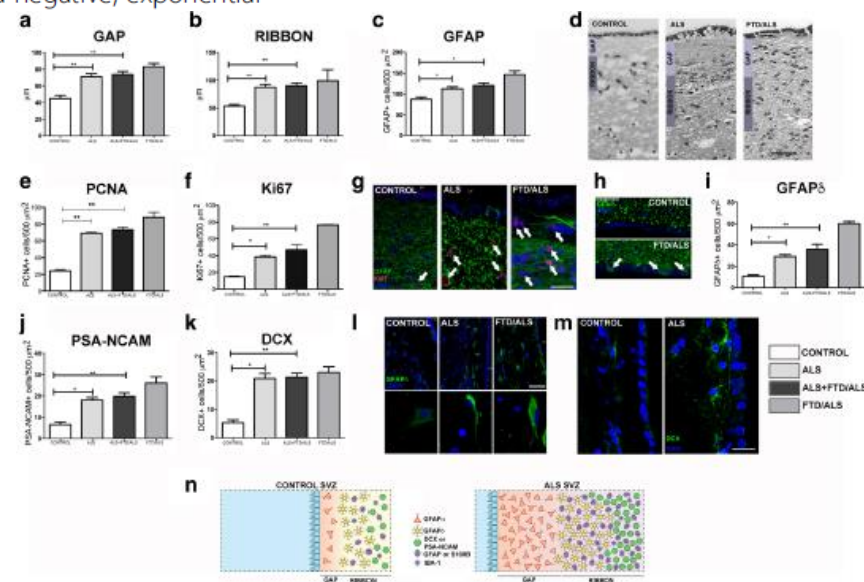


Table 3: Compounds tested for ALS treatment

Pathophysiological category	List of compounds tested for ALS
Antiapoptotic Mitochondrial impairment and aberrant calcium handling are two major components of motor neuron injury that lead to activation of the apoptotic cascade ^[58,141]	Dextramipexole (R – (+) pramipexole) ^[45] Minocycline ^[104] Pentoxifylline ^[192] Omigapil (TCH-346) ^[200] Caspase family inhibitor (fluoromethylketone) (zVAD-fmk) ^[166]
Anti-inflammatory Reactive astrocytes and microglia as well as infiltrating T lymphocytes and macrophage were found to have a main role in neurodegenerative process and neuroinflammation in ALS patients ^[248,296]	AM-1241 (aminoalkylindole family) ^[268] Celastrol ^[143] Celecoxib ^[104] EPO ^[163] Glatiramer acetate ^[193] Minocycline ^[105] Nordihydroguaiaretic acid ^[32] Arundic acid (ONO-2506) ^[68] Pioglitazone ^[144] RO-28-2653 (synthetic inhibitor of MMPs) ^[172] Rofecoxib ^[13] Thalidomide ^[282]
Anti-excitotoxicity/antiglutamatergic Excitotoxicity is mainly modulated by the release of glutamate. ALS patients have a decreased glutamate transport capacity due to loss of EAAT2 transporter receptors. This lead to increase of glutamate levels in the CSF of ALS patients ^[167,297]	Ceftriaxone ^[294] Cobalamin ^[137] Gabapentin ^[320] Lamotrigine ^[253] L-Arginine ^[128] Memantine ^[67] N-acetylated alpha-linked acidic dipeptidase ^[98] Riluzole ^[20] Talampanel ^[232] Nordihydroguaiaretic acid ^[32] Glatiramer acetate ^[193]

Pathophysiological category	List of compounds tested for ALS
Antioxidant In ALS mutations of the SOD gene reduce its superoxide dismutase activity therefore leading to elevation of free radical accumulation and oxidative stress.^[267,272,277] Several antioxidant compounds have been found to protect neurons	AeOL-10150 (Aeolus)^[226] Ammonium tetrathiomolybdate^[290] Celastrol^[143] Creatine^[108,186] Coenzyme Q10^[89] Edavarone^[328] N-acetylcysteine^[174] Olesoxime (TrO19622)^[29,30,181] R(+) pramipexole^[45] Tamoxifen^[36] Tocopherol (Vitamin E)^[74]
Anti-aggregation Mutation in SOD1 gene causes conformational instability of the encoded protein leading to the formation of aggregates. Cellular proteins aggregation, such as the Bunina bodies, is a well-known feature of ALS.^[94] Preventing these cellular aggregates can increase the survival of motor neurons	Ariclomol^[61] Scriptaid^[55] Sodium phenylbutyrate^[60] Valproate^[237] Celastrol^[143]
Neuroprotective and neurotrophic growth factor Several mechanisms such as glutamate excitotoxicity, aberrant protein aggregation, and oxidative stress lead to neurodegeneration, either loss or shrinkage of neurons, in ALS^[88,94,125] Neuroprotective drugs can help with slowing down the neuronal damage. These growth factors stimulate the growth of new neurons (neurogenesis) and the repair the damaged ones^[119,152]	BDNF^[220] Ciliary neurotrophic factor^[202] GDNF^[152,284] r-IGF-1^[278] Xaliproden^[161] VEGF^[262] EPO^[40] rh-GSF^[215] rh-HGF^[136] Rasagiline^[314]

RILUZOLE

A controlled trial of riluzole in ALS (1994)

Bensimon G. et al and ALS/riluzole Study Group

N Engl J Med 330:585-591

Estudio doble ciego (riluzole 100 mgr-placebo) 12 meses N=155

	riluzole	placebo
Supervivencia a 12 meses	74 %	58 %
forma inicio bulbar	73 %	35 %
inicio extremidades	74 %	64 %
Fin del ensayo (573 días de promedio)		
probabilidad supervivencia	49%	37 %

RILUZOLE

Dose range study of riluzole in ALS (1996)

Lacomblez L et al. And ALS/Study Group

Lancet 347: 1425-1431

Estudio doble ciego (riluzole 50, 100, o 200 mgr–placebo) N=959 18meses

		riluzole	placebo
Supervivencia	50 mgr	55.3 %	50.4 %
	100mgr	56.8 %	
	200mgr	57.8 %	

Riluzole for ALS/MND. Cochrane Database (2001)

Miller RG et al.

La mejoría de la esperanza de vida observada con riluzole es limitada entorno a los 3 y seis meses de vida

RILUZOLE

An outcome study of riluzole in ALS- a population based study in Ireland 1996-2000 (2003)

Taynor BJ et al.

J Neurol 250: 473-479

N=246	riluzole 149	no tratamiento 97	
Supervivencia	48 (149) 32 %	23 (97) 24 %	
Inicio bulbar	36 (80) 45 %	22 (57) 38 %	> 12 meses

Efecto beneficioso no se observa por encima de los 18 meses

Utilizarlo en fases precoces

EFFICACIA Y SEGURIDAD DE MASITINIB ASOCIADO A RILUZOL EN EL TRATAMIENTO DE LA E.L.A.: RESULTADOS POSITIVOS DEL ENSAYO MULTINACIONAL FASE III INICIADO EN ESPAÑA

**Jesús S. Mora^{1*}, Delia Chaverri², Javier Mascías², María Hernández²,
Saúl Marín², Yolanda Morán², Pilar Carbajo², Teresa Salas², María
Salvadó³, Raúl Domínguez⁴, Andrés Paipa⁴, Josep Gámez³, Mónica
Povedano⁴ por el Masitinib/ALS AB10015 Trial Group**

¹ Unidad de ELA, Hospital San Rafael, Madrid.

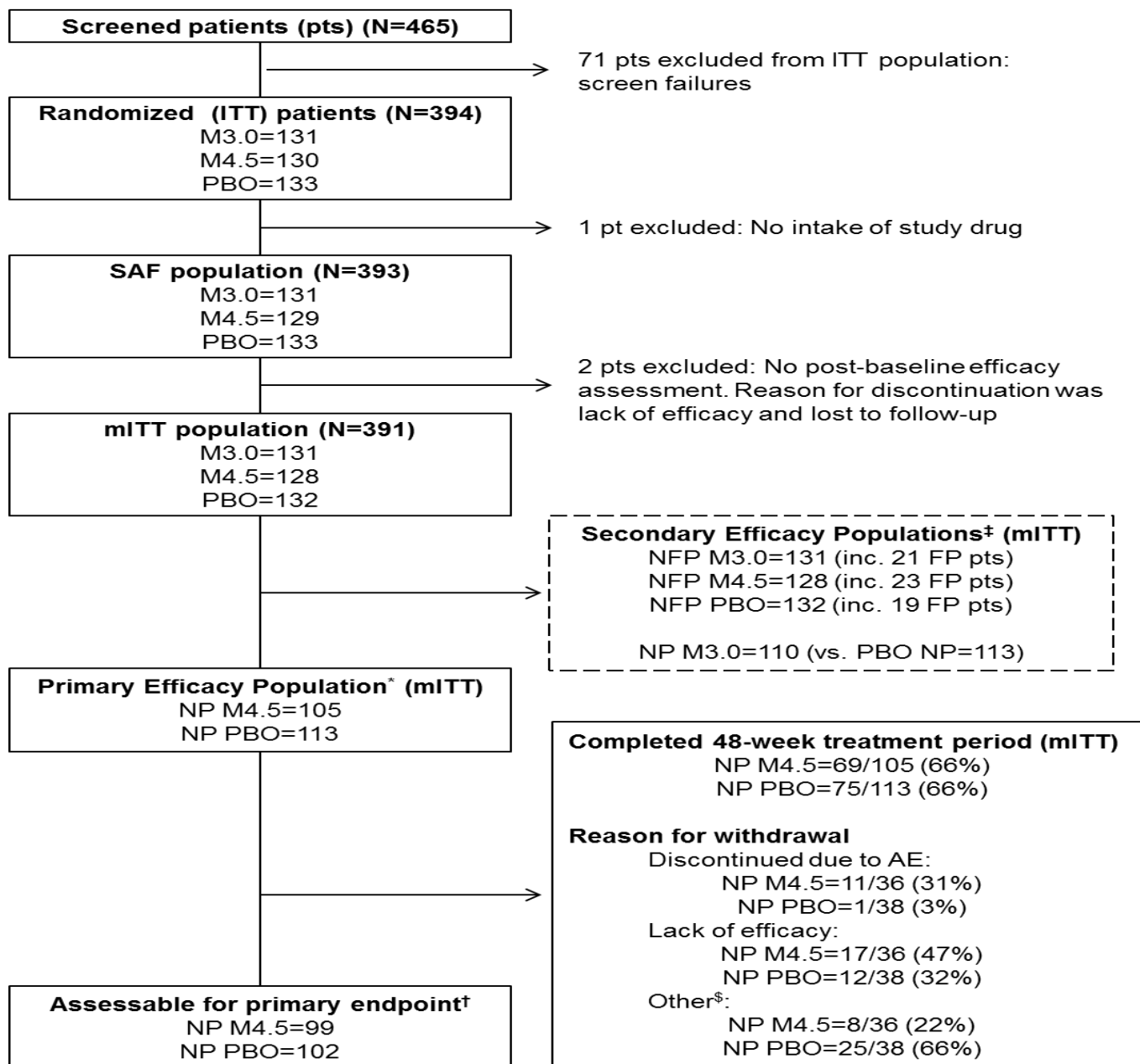
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STUDY POPULATION SUMMARY



PRIMARY ENDPOINT ANALYSIS IN PRIMARY EFFICACY POPULATION

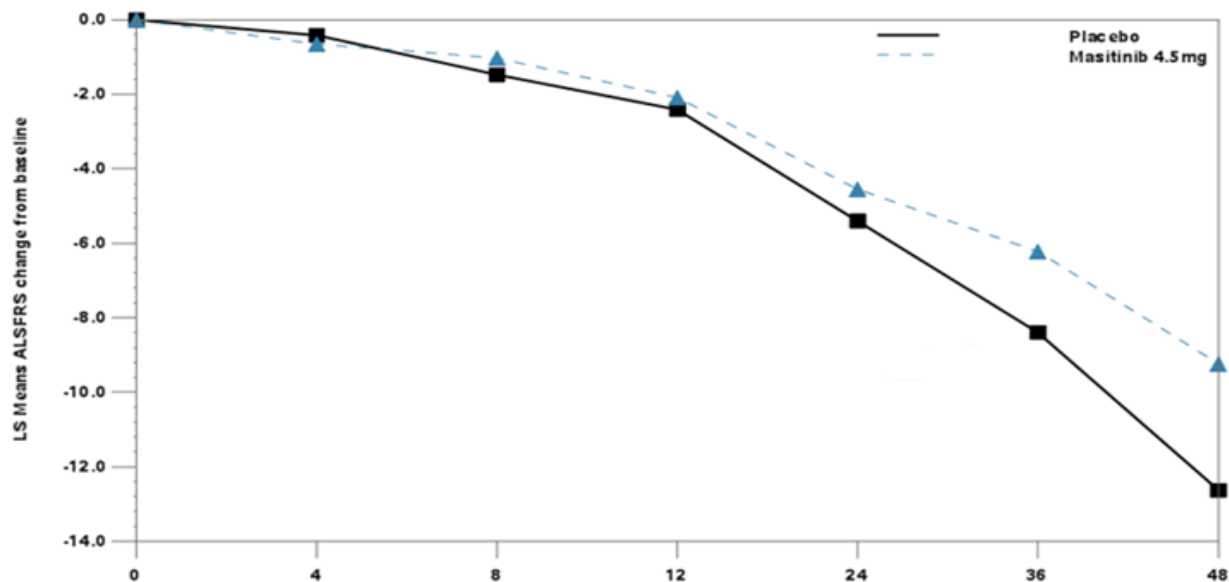
❖ Δ ALSFRS-R at w48 on the NP M4.5 cohort demonstrated significant benefit

TREATMENT GROUP	N*	LS Mean	Difference of means [95%CI]	p-value	Re- randomization p-value
Placebo + riluzole	102	-12.63	3.3878 [0.6451;6.1305]	0.0157	0.0158
Masitinib 4.5 + riluzole	99	-9.24			

❖ W0-W48 mean change: -12.6 points in placebo arm: -1.15 p/mo.

-9.2 points in masitinib 4.5 arm: -0.84 p/mo.

❖ 27% slowing of ALSFRS-R deterioration over 48-week treatment period

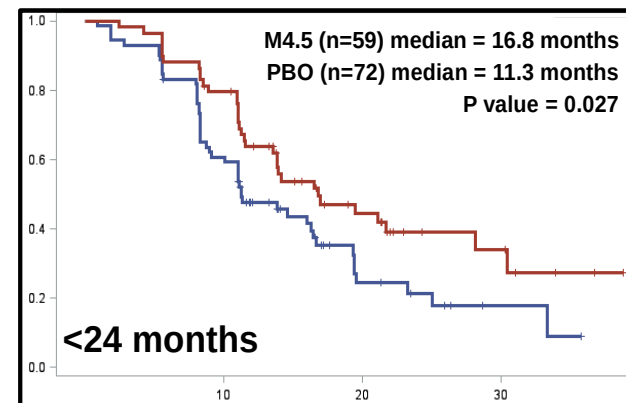
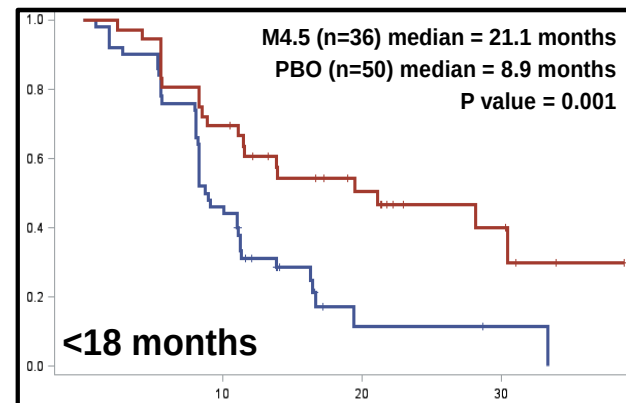


SUBGROUP ANALYSES (in primary efficacy population)

❖ Patients having milder symptoms and/or shorter duration of illness showed enhanced masitinib treatment-effect.

- Disease duration < 18 months = 32% slowing of ALSFRS-R decline
- Disease duration < 24 months = 25% slowing of ALSFRS-R decline
- Score of ≥ 2 for each ALSFRS-R item and less than 24-month duration of illness = 45% slowing of ALSFRS-R decline

❖ Benefit of early initiation of masitinib treatment also seen in survival-to-event analysis (M4.5 = red line; PBO = blue line)



❖ Interpretation: Early initiation of masitinib treatment carries greater benefit

- ❖ **Oral Masitinib at 4.5 mg/kg/day demonstrated a significant and clinically meaningful benefit in ALS patients with a baseline progression rate of <1.1 points/month at the ALSFRS-R**
 - 27% slowing of ALSFRS-R deterioration; P=0.0158
 - 29% slowing of deterioration in quality-of-life (ALSAQ-40); P=0.0078
 - 22% slowing of deterioration in respiratory function (FVC); P=0.0296
 - 25% delay in disease progression (survival-to-event); P=0.0159
- ❖ **Benefit appears related to drug dose, disease duration, and symptoms severity at onset of therapy**
- ❖ **Safety was acceptable, hepatic control recommended**

THE POSITIVE BENEFIT-RISK BALANCE OF STUDY AB10015 SIGNALS THAT MASITINIB PROVIDES A SIGNIFICANT NEW THERAPEUTIC OPTION IN AN ALS POPULATION



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