A proposal for new criteria

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Gold Coast Criteria for Diagnosing ALS

Developed at a consensus conference held by IFCN, WFN, ALS Association, and MND Association in Gold Coast, Australia, in 2019

Documented progressive motor impairment that was preceded by normal motor function

Impairment must be documented by history or repeated clinical assessment

\+

Upper and lower motor neuron dysfunction in ≥ 1 body region or lower motor neuron dysfunction in ≥ 2 body regions

If only 1 body region is affected, upper and lower motor neuron dysfunction must both be present

\+

Investigations that have excluded other diseases processes

Nerve conduction studies, needle EMG, imaging, fluid studies (blood or CSF), or other modalities as clinically appropriate

Shefner JM, et al. *Clin Neurophysiol*. 2020;131:1975-1978.

ed criteria do not include:

o extramotor
gns/symptoms
No genetics
lo imaging or
biomarkers

Shefner JM, et al. *Clin Neurophysiol*. 2020;131:1975-1978.

Criteria for diagnosis of ALS.

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and
2. Presence of upper[1] and lower[2] motor neuron dysfunction in at least 1 body region[3] , (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least 2 body regions, and
3. Investigations[4] excluding other disease processes

Footnotes:

[1]Upper motor neuron dysfunction implies at least one of the following:

1. Increased deep tendon reflexes, including the presence of a reflex in a clinically weak and wasted muscle, or spread to adjacent muscles
2. Presence of pathological reflexes, including Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex.
3. Increase in velocity-dependent tone (spasticity)
4. Slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or Parkinsonian features

[2]Lower motor neuron dysfunction in a given muscle requires either:

Clinical examination evidence of

Muscle weakness, and
Muscle wasting

or

EMG abnormalities that must include:

Both evidence of chronic neurogenic change, defined by large motor unit potentials of increased duration and/or increased amplitude, with polyphasia and motor unit instability regarded as supportive but not obligatory evidence.

And evidence of ongoing denervation including
Fibrillation potentials or positive sharp waves, or
fasciculation potentials

[3]Body regions are defined as bulbar, cervical, thoracic and lumbosacral. To be classified as an involved region with respect to lower motor neuron involvement, there must be abnormalities in two limb muscles innervated by different roots and nerves, or one bulbar muscle, or one thoracic muscle either by clinical examination or by EMG.

[4]The appropriate investigations depend on the clinical presentation, and may include nerve conduction studies and needle EMG, MRI or other imaging, fluid studies of blood or CSF, or other modalities as clinically necessary.

Neurodegeneration

RESEARCH PAPER

Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis

Adriano Chiò,[1] Edward R Hammond,[2] Gabriele Mora,[3] Virginio Bonito,[4] Graziella Filippini[5]

J Neurol Neurosurg Psychiatry 2015;**86**:38–44. doi:10.1136/jnnp-2013-306589

MITOS staging system

Table 1 Functional domains and stages

ALSFRS domain	Item	Score	Functional score*
Movement (walking/self-care)†	8	4 Normal	0
	Walking	3 Early ambulation difficulties	
		2 Walks with assistance	
		1 Non-ambulatory functional movement only	1
	OR	0 No purposeful leg movement	
	6	4 Normal function	0
	Dressing and hygiene	3 Independent and complete self-care with effort or decreased efficiency	
		2 Intermittent assistance or substitute methods	
		1 Needs attendant for self-care	1
		0 Total dependence	
Swallowing	3	4 Normal eating habits	0
	Swallowing	3 Early eating problems; occasional choking	
		2 Dietary consistency changes	
		1 Needs supplemental tube feeding	1
		0 NPO (exclusively parenteral or enteral feeding)	
Communicating†	1	4 Normal speech processes	0
	Speech	3 Detectable speech with disturbances	
		2 Intelligible with repeating	
		1 Speech combined with non-vocal communication	1
	AND	0 Loss of useful speech	
	4	4 Normal	0
	Handwriting	3 Slow or sloppy; all words are legible	
		2 Not all words are legible	
		1 Able to grip pen but unable to write	1
		0 Unable to grip pen	
Breathing†	10	4 None	0
	Dyspnea	3 Occurs when walking	
		2 Occurs with one or more of: eating, bathing, dressing	
		1 Occurs at rest, difficulty breathing when either sitting or lying	1
	OR	0 Significant difficulty, considering using mechanical respiratory support	
	12	4 None	0
	Respiratory insufficiency	3 Intermittent use of NIPPV	
		2 Continuous use of NIPPV during the night	1
		1 Continuous use of NIPPV during the night and day	
		0 Invasive mechanical ventilation by intubation or tracheostomy	
ALS-MITOS	Stage	Functional domains lost	
	0	None	
	1	1 domain	
	2	2 domains	
	3	3 domains	
	4	4 domains	
	5	Death	

*Staging determined by the sum of functional score of 1 for each domain.
†Where two items were used, scoring was based on either or both item scores as indicated.
ALFSRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; ALS-MITOS, Amyotrophic Lateral Sclerosis Milano-Torino Staging; NIPPV, nasal intermittent positive pressure ventilation; NPO, nothing by mouth.

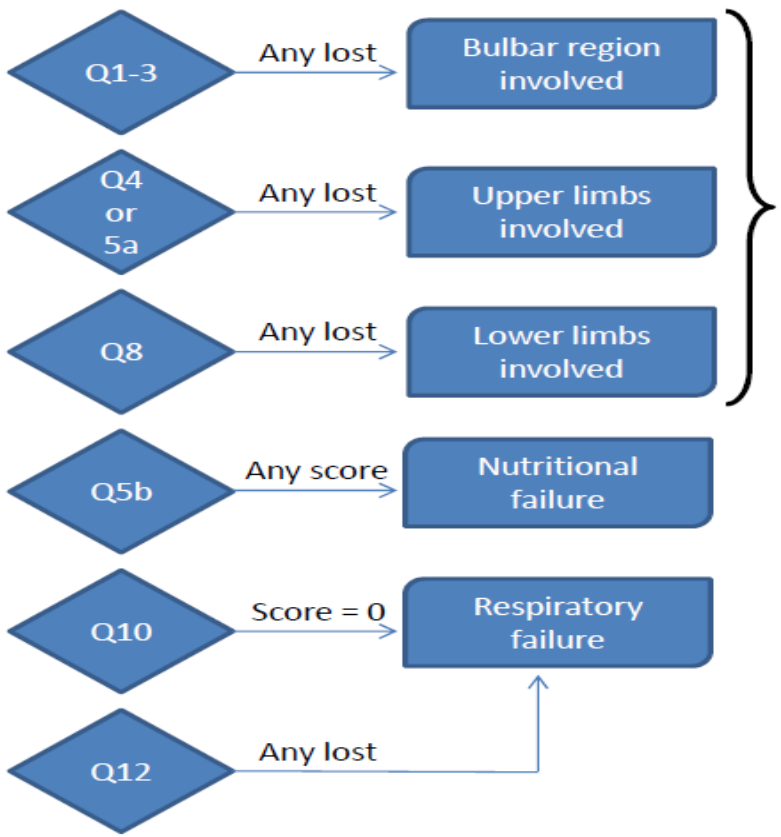
doi:10.1093/brain/awr351 Brain 2012: 135; 847–852 | 847

BRAIN
A JOURNAL OF NEUROLOGY

A proposed staging system for amyotrophic lateral sclerosis

Jose C. Roche,[1,2] Ricardo Rojas-Garcia,[1,3] Kirsten M. Scott,[1] William Scotton,[1] Catherine E. Ellis,[4] Rachel Burman,[5] Lokesh Wijesekera,[1] Martin R. Turner,[6] P. Nigel Leigh,[1,7] Christopher E. Shaw[1] and Ammar Al-Chalabi[1]

Mapping ALSFRS to King's Stage



92% correlation with actual stage

N = 103 scores

Count regions = Stage 1, 2, 3

Stage 4a

Stage 4b

Data from King's College Hospital Motor Nerve Clinic

Balendra, ALS and FTD 2014

Table 4 King's stages according to NBRI at diagnosis

N.of body regions					
King's stages	**1**	**2**	**3**	**4**	**Total**
1	483	39	6	0	528
%Col	98.2%	13.5%	3.1%	0.0%	49.7%
%Row	91.5%	7.4%	1.1%	0.0%	100.0%
2	5	240	52	3	300
%Col	1.0%	83.3%	26.5%	3.5%	28.2%
%Row	1.7%	80.0%	17.3%	1.0%	100.0%
3	0	4	110	57	171
%Col	0.0%	1.4%	56.1%	66.3%	16.1%
%Row	0.0%	2.3%	64.3%	33.3%	100.0%
4	4	5	28	26	63
%Col	0.8%	1.7%	14.3%	30.2%	5.9%
%Row	6.3%	7.9%	44.4%	41.3%	100.0%
Total	492	288	196	86	1062
%Col	100.0%	100.0%	100.0%	100.0%	100.0%
%Row	46.3%	27.1%	18.5%	8.1%	100.0%

NBRI, number of body regions involved.

ORIGINAL RESEARCH

Regional spreading of symptoms at diagnosis as a prognostic marker in amyotrophic lateral sclerosis: a population-based study

Umberto Manera ,[1] Andrea Calvo ,[1] Margherita Daviddi,[1] Antonio Canosa ,[1] Rosario Vasta ,[1] Maria Claudia Torrieri,[1] Maurizio Grassano,[1] Maura Brunetti,[1] Sandra D'Alfonso,[2] Lucia Corrado,[2] Fabiola De Marchi,[3] Cristina Moglia,[1] Fabrizio D'Ovidio ,[1] Gabriele Mora,[4] Letizia Mazzini,[3] Adriano Chiò[1,5]

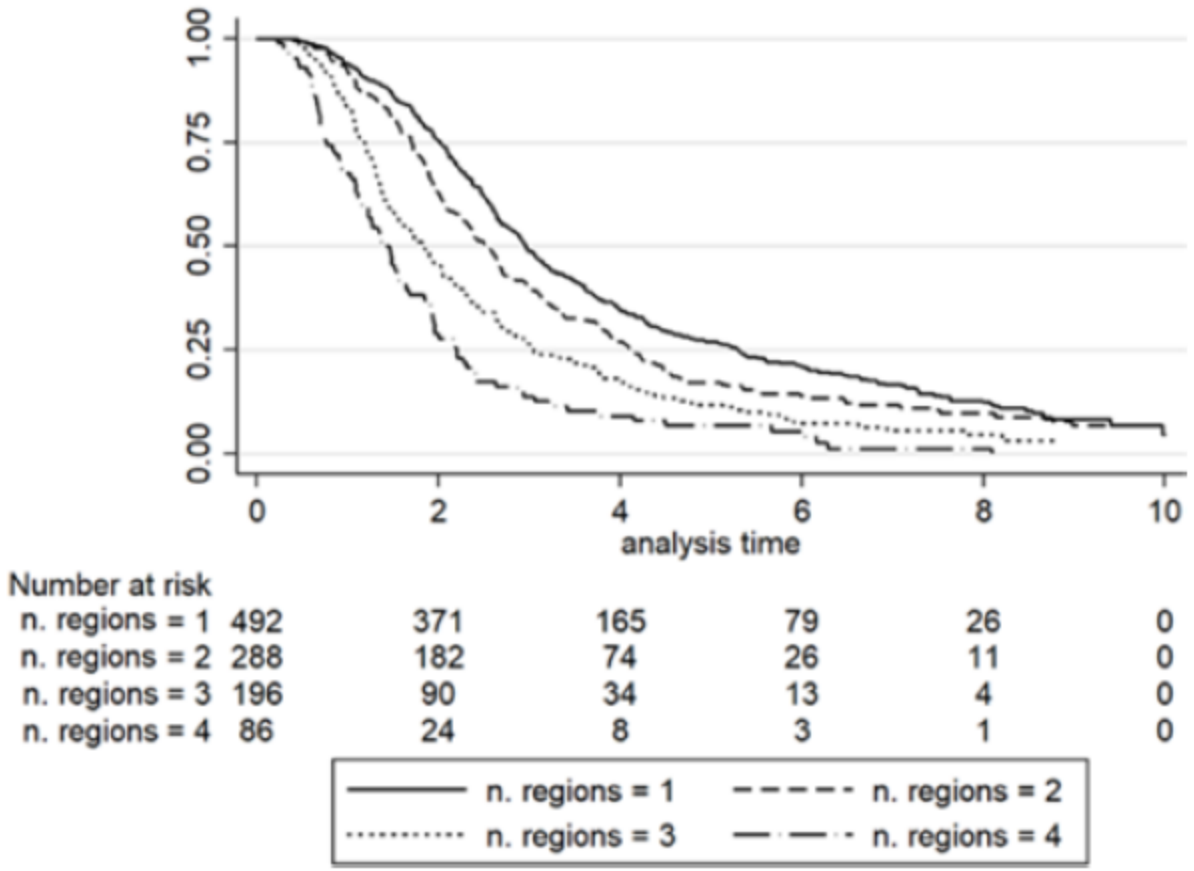


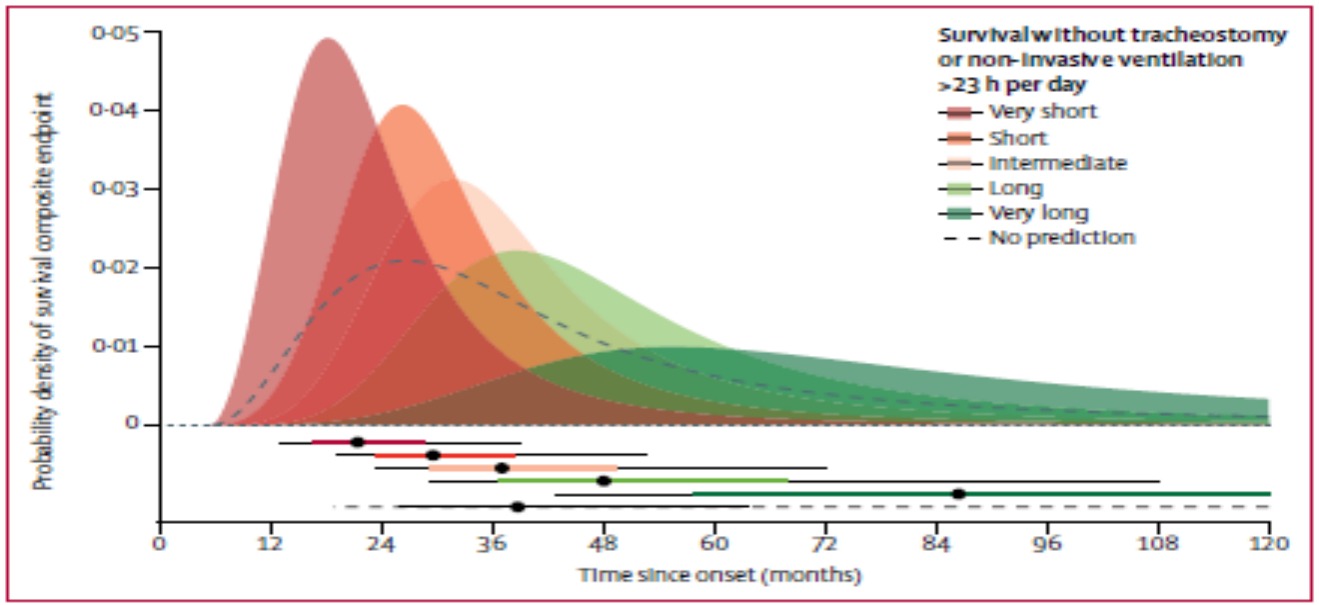
Figure 1 Kaplan-Meier curve of patients with ALS by NBRI at diagnosis. ALS, amyotrophic lateral sclerosis; NBRI, number of body regions involved.

Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model

Henk-Jan Westeneng, Thomas P A Debray, Anne E Visser, Ruben P A van Eijk, James P K Rooney, Andrea Calvo, Sarah Martin, Christopher J McDermott, Alexander G Thompson, Susana Pinto, Xenia Kobeleva, Angela Rosenbohm, Beatrice Stubendorff, Helma Sommer, Bas M Middelkoop, Annelot M Dekker, Joke J F A van Vugt, Wouter van Rheenen, Alice Vajda, Mark Heverin, Mbombe Kazoka, Hannah Hollinger, Marta Gromicho, Sonja Körner, Thomas M Ringer, Annekathrin Rödiger, Anne Gunkel, Christopher E Shaw, Annelien L Bredenoord, Michael A van Es, Philippe Corcia, Philippe Couratier, Markus Weber, Julian Grosskreutz, Albert C Ludolph, Susanne Petri, Mamede de Carvalho, Philip Van Damme, Kevin Talbot, Martin R Turner, Pamela J Shaw, Ammar Al-Chalabi, Adriano Chiò, Orla Hardiman, Karel G M Moons, Jan H Veldink, Leonard H van den Berg

Lancet Neurol 2018

Published Online
March 26, 2017



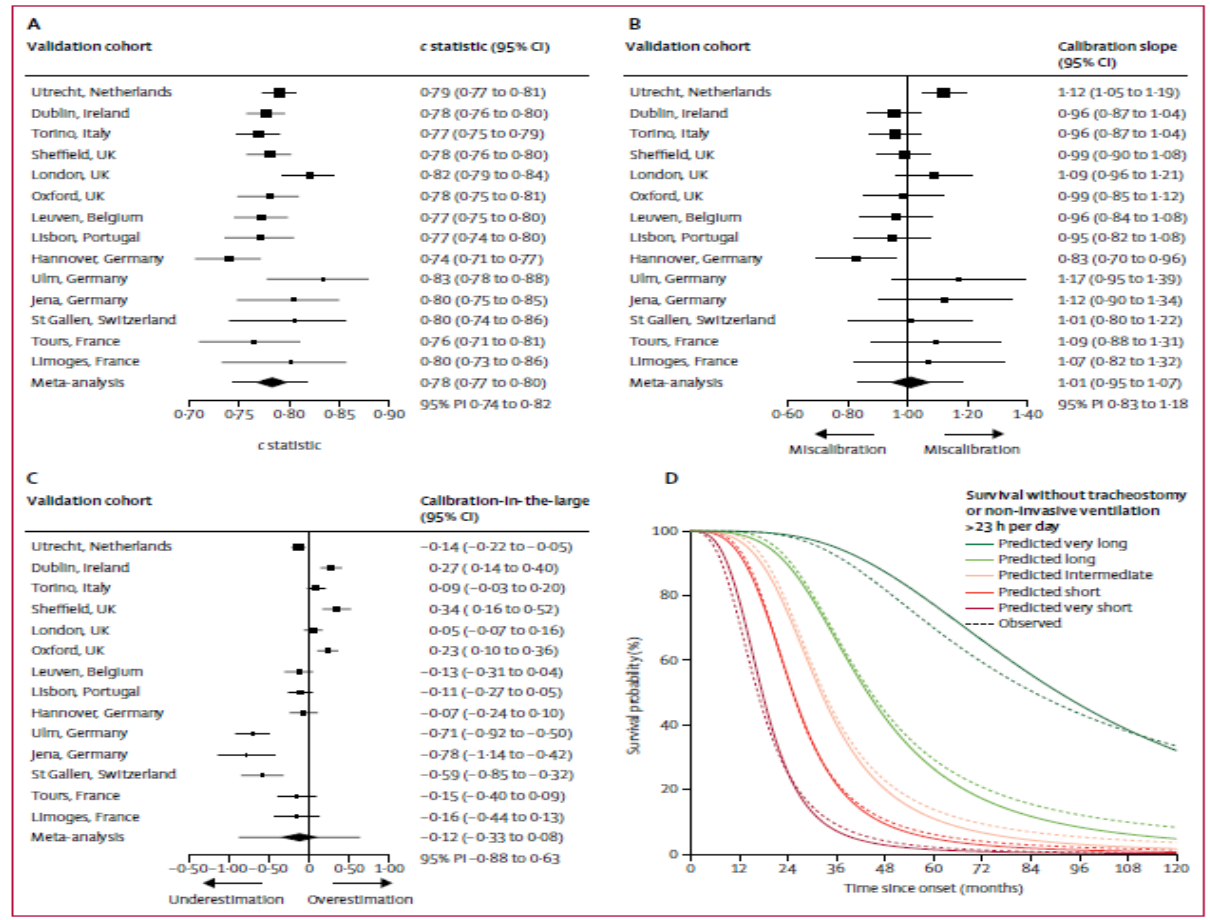


Figure 1: **Univariate meta-analysis of predictive performance**
Panel A shows the random-effects meta-analysis of discrimination as measured with the *c* statistic (time-dependent receiver operator characteristic [ROC] curves in the appendix). Panels B and C show the random-effects meta-analysis of calibration as measured with calibration slope (B) and calibration-in-the-large (C). A calibration slope of 1 in combination with a calibration-in-the-large of 0 indicated good overall calibration (calibration slope <1: predictions are too extreme; calibration slope >1: predictions are too similar; further details in the appendix). The black diamonds indicate the mean (95% CI) of the predictive accuracy. 95% prediction intervals (PI), which indicate predicted accuracy of the model in a single new dataset or patient, are presented as a numeric range (below the 95% CI). Panel D is the visual translation of A–C in prognostic curves showing the agreement between predicted and observed probability of reaching the composite endpoint as well as indicating good discriminative power of the model. The curves also illustrate the possibility to stratify patients in different groups based on their predicted prognosis on the day of diagnosis. Five equal-sized groups were created based on predicted time to our composite endpoint. Omitted cohort label indicates the cohort left out of the internal–external cross-validation, which was done once for all 14 different cohorts.

ARTICLE

ALS phenotype is influenced by age, sex, and genetics

A population-based study

Adriano Chiò, MD, FAAN, Cristina Moglia, MD, PhD, Antonio Canosa, MD, PhD, Umberto Manera, MD, Fabrizio D'Ovidio, PhD, Rosario Vasta, MD, Maurizio Grassano, MD, Maura Brunetti, BSc, Marco Barberis, BSc, Lucia Corrado, PhD, Sandra D'Alfonso, PhD, Barbara Iazzolino, PsyD, Laura Peotta, PsyD, Maria Francesca Sarnelli, PsyD, Valentina Solara, PsyD, Jean Pierre Zucchetti, MS, Fabiola De Marchi, MD, Letizia Mazzini, MD,* Gabriele Mora, MD,* and Andrea Calvo, MD, PhD*

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Neurology® 2020;94:e802-e810. doi:10.1212/WNL.0000000000008869

I fattori determinanti del fenotipo motorio: età, sesso e genetica

Figure 2 Graphic representation of odds ratios (ORs) of age classes for the phenotypes of amyotrophic lateral sclerosis

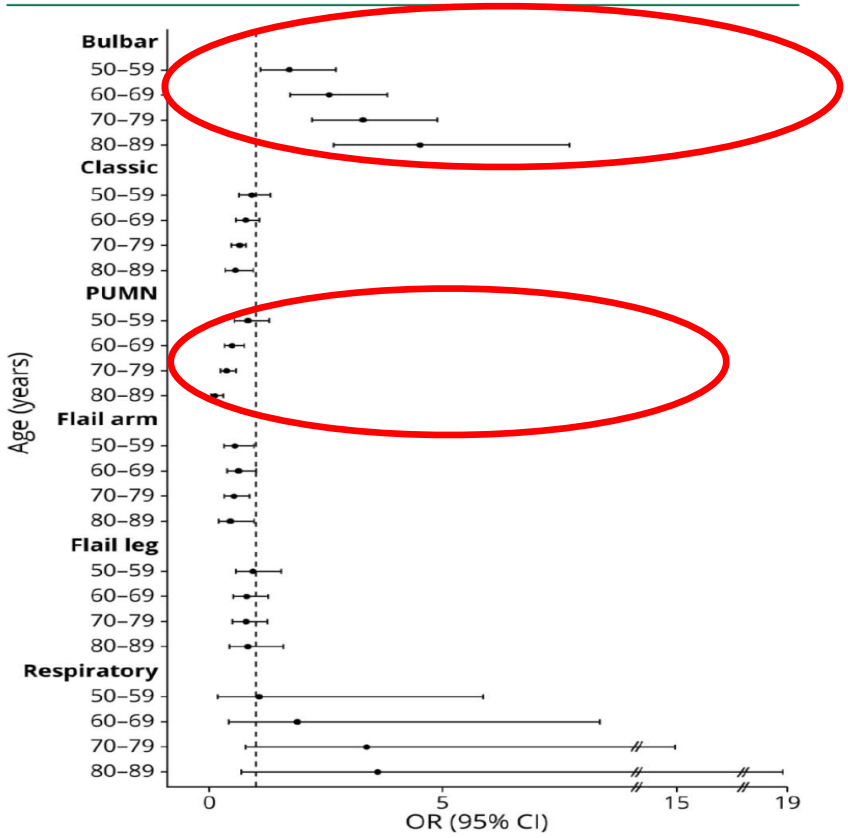
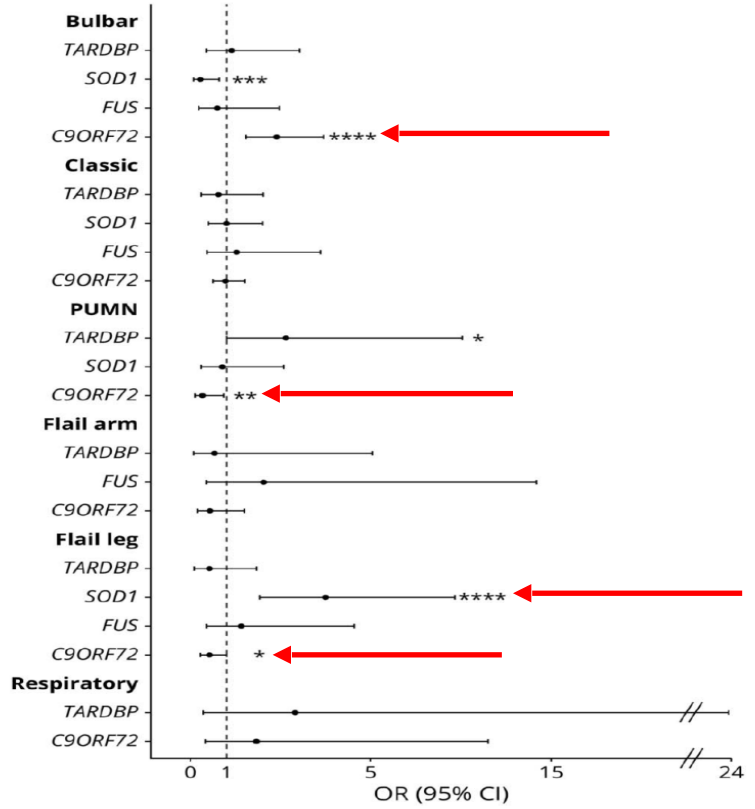


Figure 3 Graphic representation of odds ratios (ORs) of gene mutations for the phenotypes of amyotrophic lateral sclerosis



Lei è un/a paziente con SLA/MND o una persona che lo/a assiste?

Faccia clic qui per condividere le Sue esperienze riguardo il sondaggio europeo sulla SLA per aiutare a guidare lo sviluppo di nuovi farmaci e servizi per la SLA

Epidemiologia genetica della SLA

Eterogeneità della SLA fra le popolazioni: epidemiologica genetica della SLA (sALS+fALS)

	# of cases (fALS+sALS)	SOD1	TARDBP	FUS	C9ORF72	Other mutations
Ireland (Kenna et al, 2013)	444	0	0.5%	0.5%	8.8%	4.4% *
Italy (Chiò et al, 2012)	475	2.1%	1.5%	0.2%	6.7%	0.2% **
Netherlands (van Blitterswijk et al, 2012)	1289	0.2%	1.0%	0.7%	9.5%	0.6% +
Scotland ^ (Black et al, 2017)	441	5.2%	0.9%	0	10.0%	1.6% ^^
Sardinia (Borghero et al, 2014)	375	0.9%	26.7%	-	13.6%	1.0% §

Le espansioni di *C9ORF72* sono più rare in Cina e Giappone, ma non disponiamo di studi sistematici

Logroscino & Chiò, Oxford Textbook of Neurological and Neuropsychiatric Epidemiology, in press

Neurobiology of Aging 35 (2014) 2423.e1–2423.e6

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Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Extensive molecular genetic survey of Taiwanese patients with amyotrophic lateral sclerosis

Bing-Wen Soong [a,b,c], Kon-Ping Lin [a,b], Yuh-Cherng Guo [d,e], Chou-Ching K. Lin [f,g], Pei-Chien Tsai [a,c], Yi-Chu Liao [a,b], Yi-Chun Lu [a], Shuu-Jiun Wang [a,b,c,h], Ching-Piao Tsai [a,b,*], Yi-Chung Lee [a,b,c,*]

Table 1
Mutational spectrum in the 161 unrelated Taiwanese patients with ALS

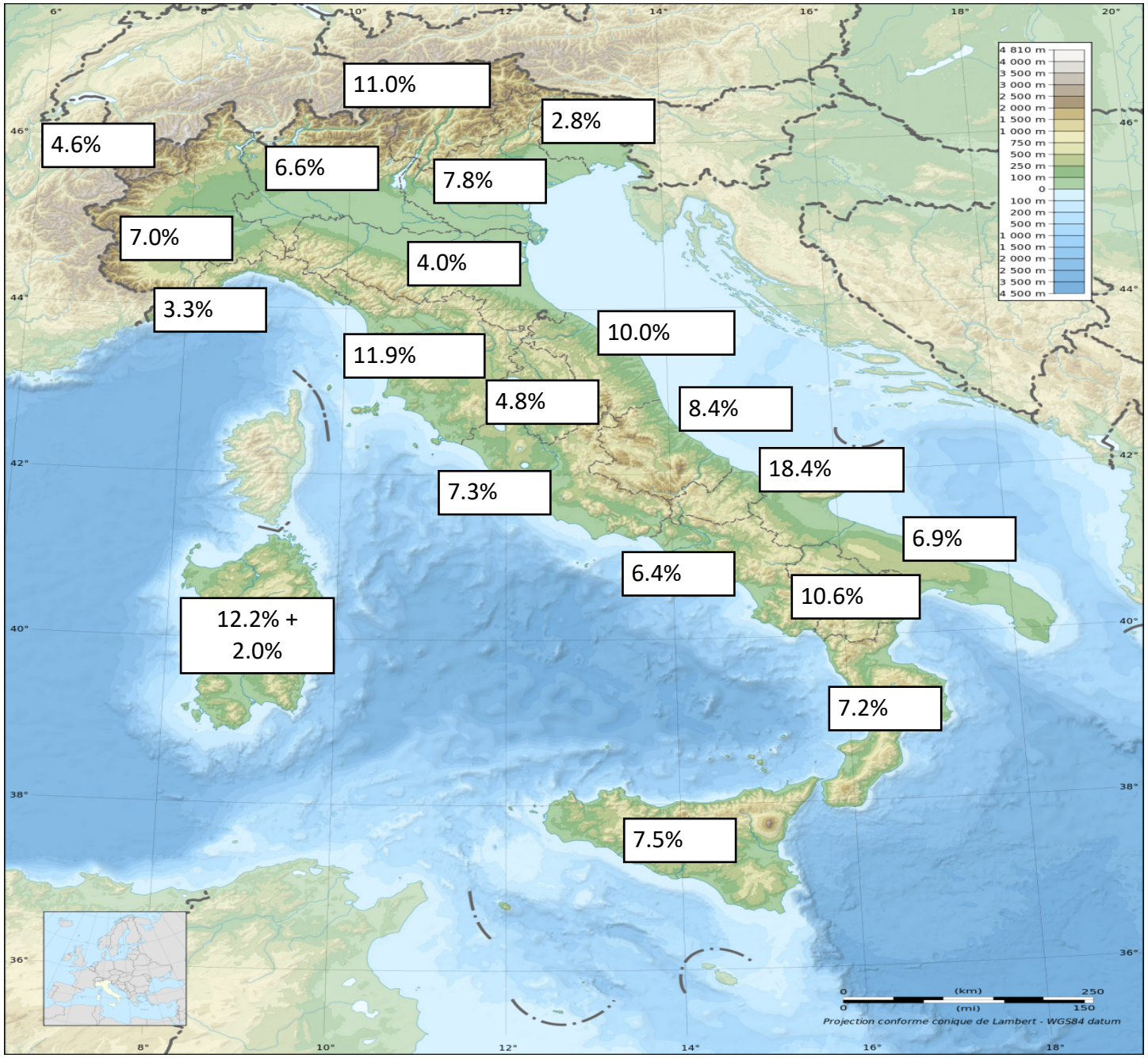
Gene	FALS (n = 30)		SALS (n = 131)		FALS + SALS (n = 161)
	Number (%)	Mutation (no. of patients)	n (%)	Mutation (no. of patients)	n (%)
SOD1	8 (26.7)	T137R (2), L8V (1), G10A (1)[a], D83N (1)[a], G85R (1), L106F (1), G138E (1)	4 (3.1)	G16S (1), G37R (1), C111Y (1), T137R (1)	12 (7.5)
TARDBP	7 (23.3)	M337V (4), G348V (1), N378D (1), I383V (1)	0		7 (4.3)
C9ORF72	5 (16.7)	GGGGCC repeat expansion	2 (1.5)	GGGGCC repeat expansion	7 (4.3)
FUS	2 (6.7)	H517D (1), R521H (1)	2 (1.5)	H517D (1), R521H (1)	4 (2.5)
ATXN2	0		2 (1.5)	32 and 33 CAG repeats	2 (1.2)
OPTN	0		1 (0.8)	L494W (1)[a]	1 (0.6)
Total	22 (73.3)		11 (8.4)		33 (20.5)
Mutation not identified	8 (26.7)		120 (91.6)		128 (79.5)

No patient was found to have a mutation in *VCP*, *UBQLN2*, *SQSTM1*, *PFN1*, *HNRNPA1* or *HNRNPA2/B1* genes.
Key: ALS, amyotrophic lateral sclerosis; FALS, familial ALS; SALS, sporadic ALS.
[a] Novel mutations.

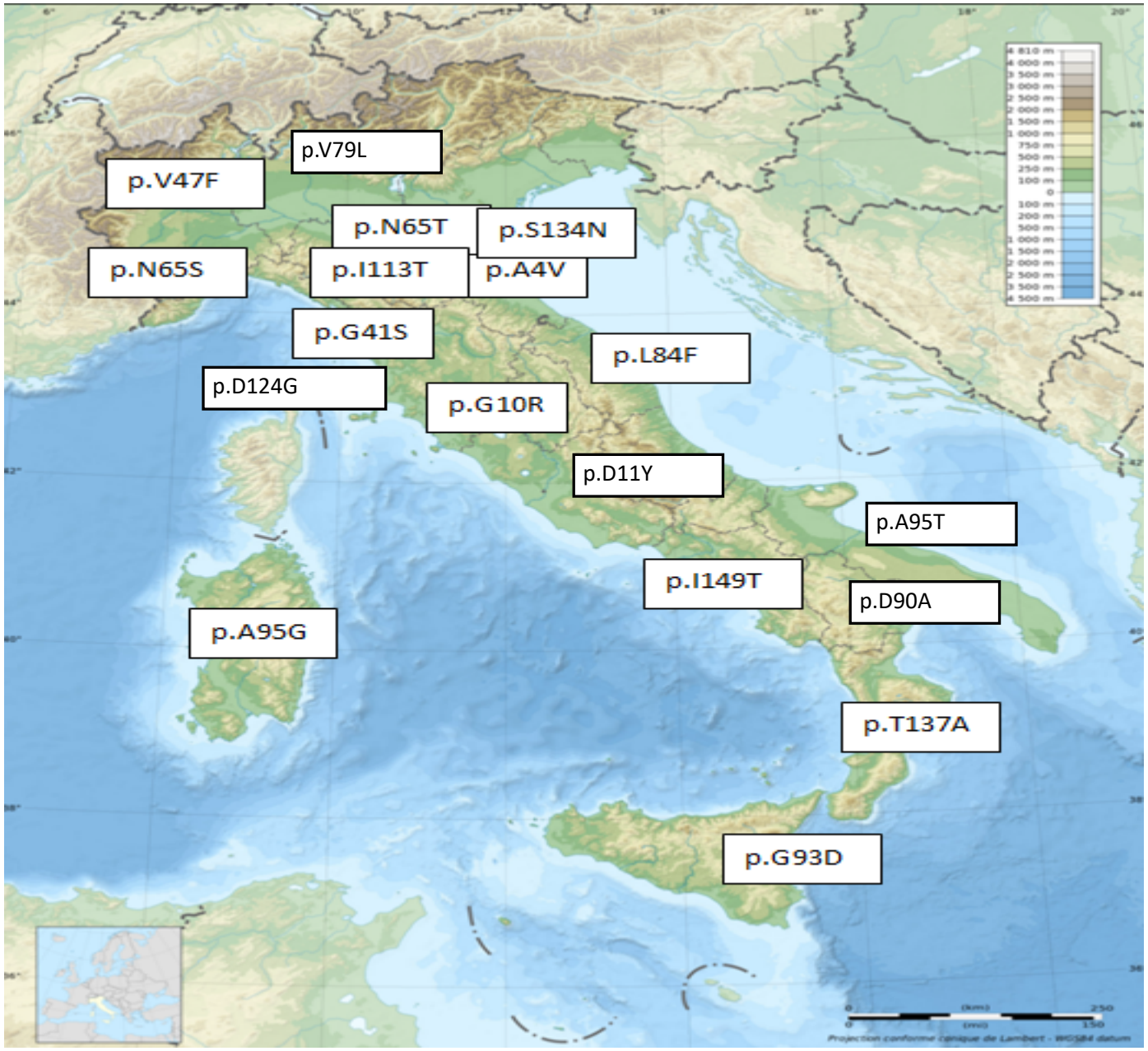
La collaborazione ITALSGEN – SLAGEN: la mappatura della SLA in Italia

- Frequenza di espansioni GGGGCC di *C9orf72*

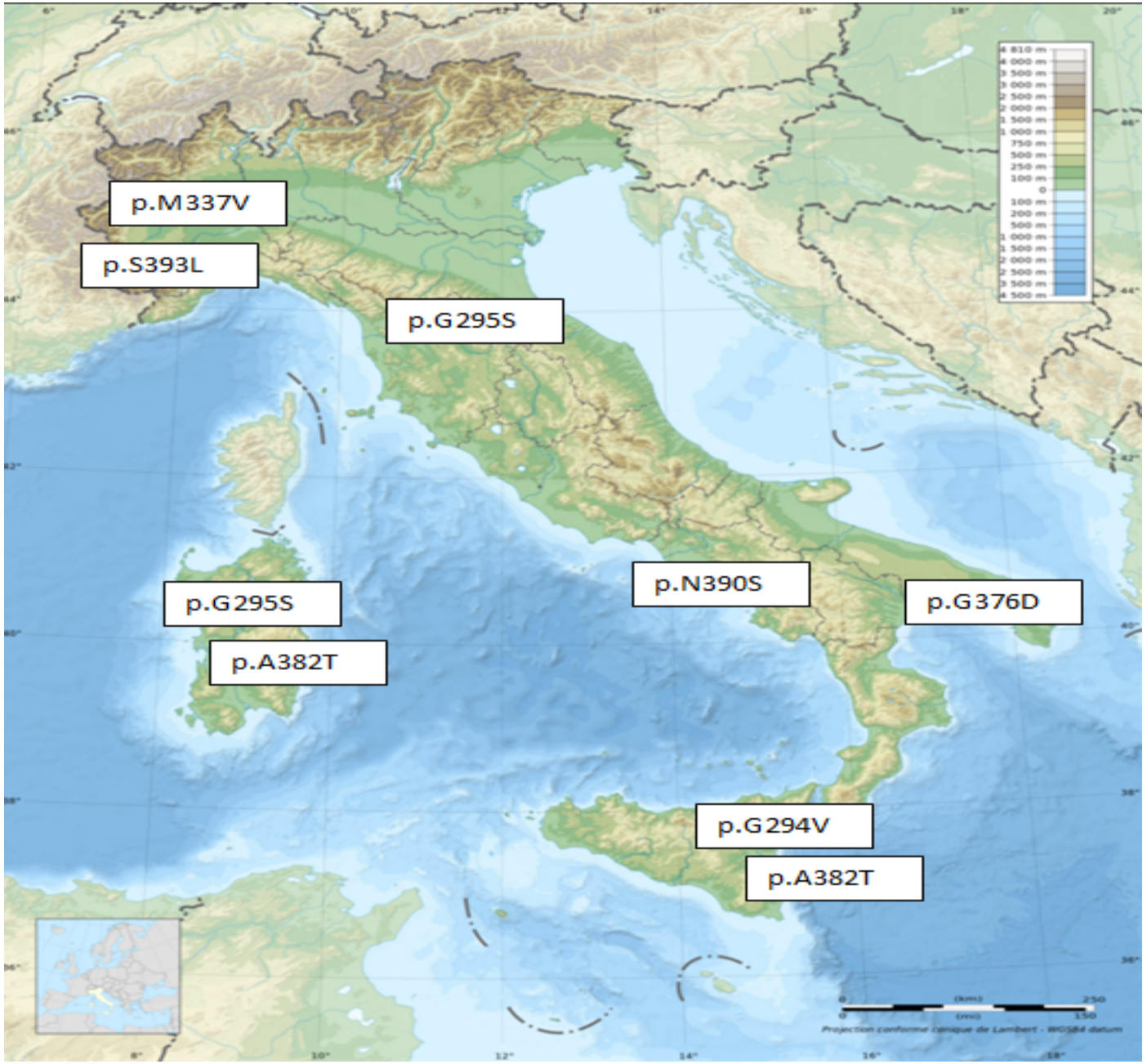
- 567 casi italiani



- Mutazioni *SOD1*
- 233 casi

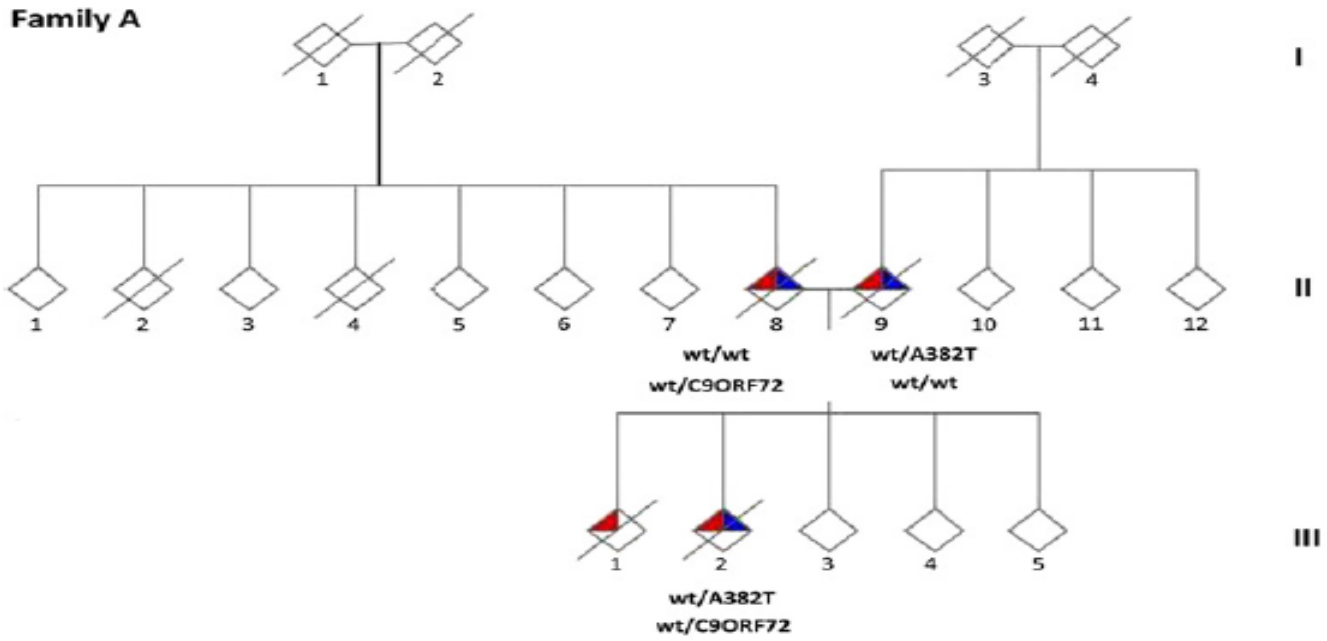


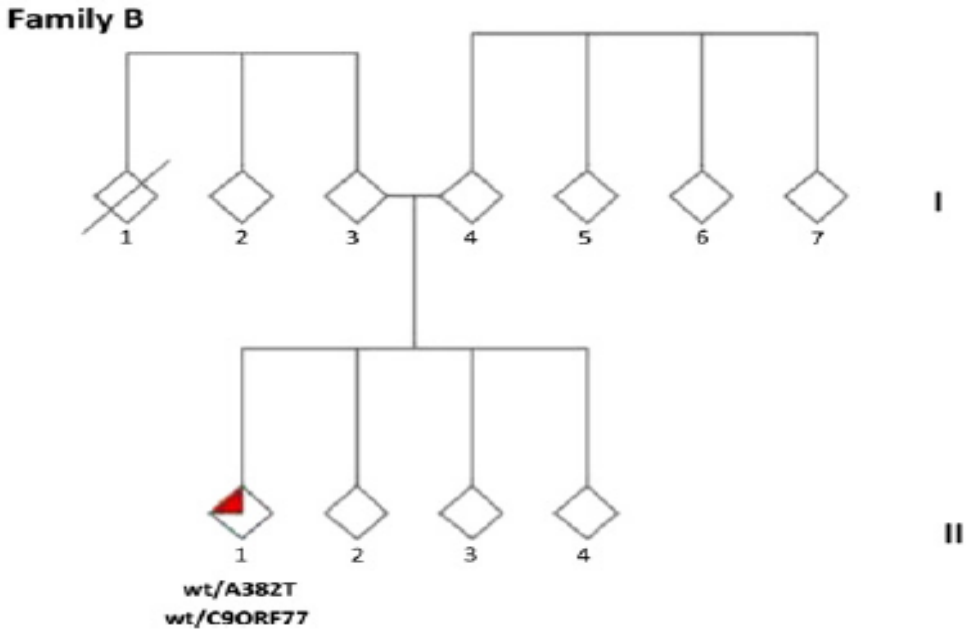
- Mutazioni *TARDBP*
- 102 casi



Oligogenicità della SLA: troppo è davvero troppo?

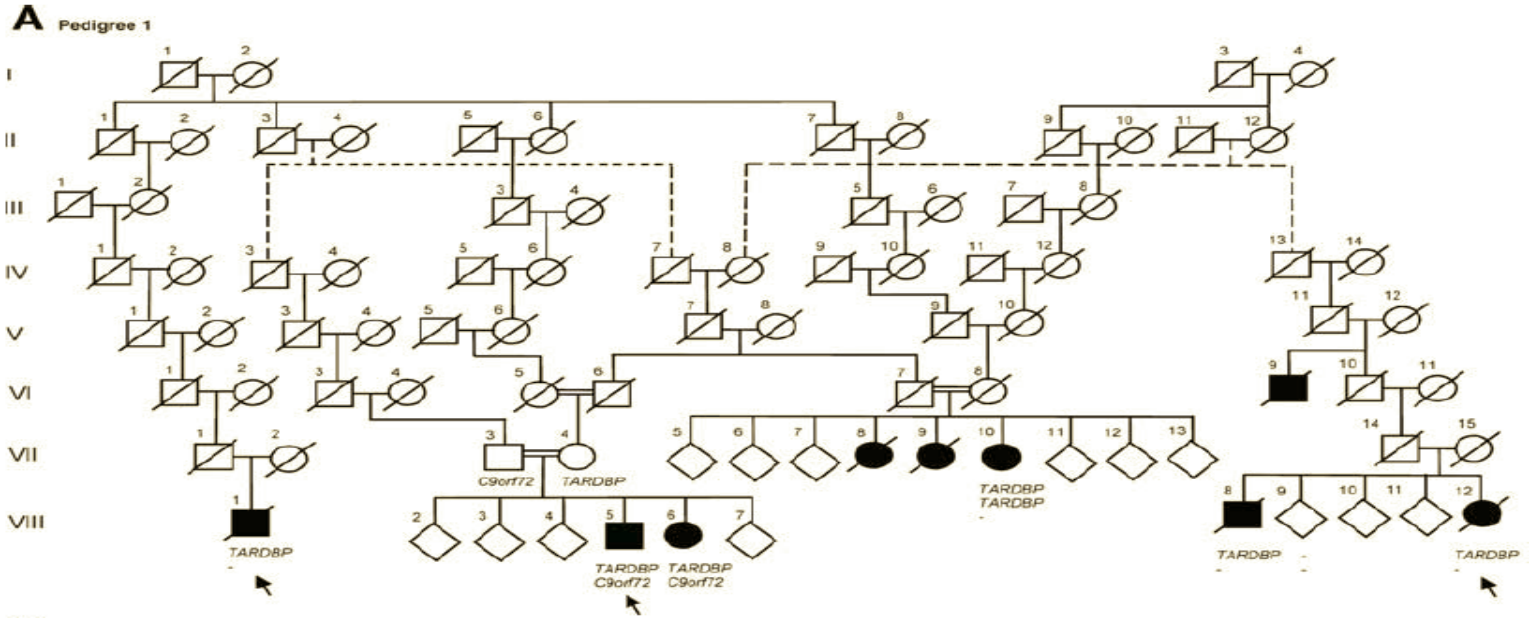
Casi di SLA portatori di espansione di *C9ORF72* e mutazione missenso p.A382Tdi *TARDBP*



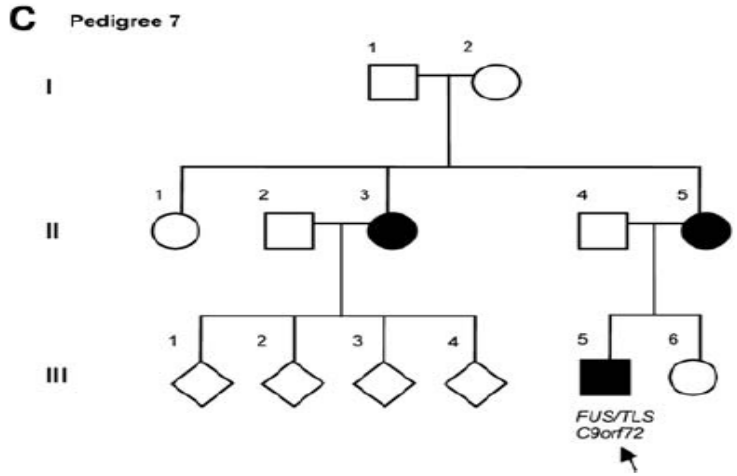


Chiò et al, J Neurol Neurosurg Psychiatry 2012

Casi portatori di espansione di *C9ORF72* e mutazioni missenso di *TARDBP o FUS*



***C9orf72* and *TARDBP*: p.N352S**



C9orf72 and FUS p.Q210H

Van Blitterswijk et al, Human Mol Genet 2012

Table 2. ALS/FTD patients carrying double mutations[a]

Variant 1	Variant 2/3	ALS/FTD	Age at onset	Refs
C9orf72 exp	TARDBP p.A382T	FALS/FTD	43–35	[109]
C9orf72 exp	TARDBP p.A321V	FALS	37	[110]
C9orf72 exp	TARDBP p.N352S	FALS	42–47	[113]
C9orf72 exp	TARDBP p.A382T	FALS	47	[112]
C9orf72 exp	TARDBP p.S292del	Familial FTD	54–47	[115]
C9orf72 exp	TARDBP p.A382T	FALS/FTD	43.8 (median)	[114]
C9orf72 exp	TARDBP p.N267S	Familial FTD		[116]
C9orf72 exp	FUS p.Q210H	FALS	58	[113]
C9orf72 exp	FUS p.G174del	FALS	62	[110]
C9orf72 exp	FUS p.R521C	FALS	40	[111]
C9orf72 exp	SOD1 p.D110Y	FALS	59	[111]
C9orf72 exp	SOD1 p.D90A	FALS	51	[113]
C9orf72 exp	GRN p.Y294C	Familial FTD	64	[117]
C9orf72 exp	GRN p.C466LfsX46	Familial FTD	52	[118]
C9orf72 exp	GRN p.R493X	Familial FTD	50	[118]
C9orf72 exp	GRN p.R493X	PFNA	62	[119]
C9orf72 exp	GRN p. C31fs	Familial FTD	59.5 (mean)	[120]
C9orf72 exp	ANG p.I46V	SALS	38	[20]
C9orf72 exp	ANG p.K17I	FALS	47	[111]
C9orf72 exp	OPTN p.E322K	FALS	50	[110]
C9orf72 exp	OPTN p.D128EfsX22	FALS	46	[111]
C9orf72 exp	SQSTM1 p.R212C	FALS/FTD	63	[75]
C9orf72 exp	SQSTM1 p.V153I	FALS		
C9orf72 exp	UBQLN2 p.G502_I504del	FALS	52	[111]
C9orf72 exp	PRPH p.R133P	SALS	70	[112]
C9orf72 exp	PSEN2 p.I146V	Familial FTD	68	[117]
C9orf72 exp	MAPT p.P301L	Familial FTD	53	[118]
C9orf72 exp	VAPB p.V234I	FALS	65	[113]
C9orf72 exp	DAO p.R38H	FALS	42	[111]
C9orf72 exp	DCTN1 p.I196V	FALS		[124]
C9orf72 exp	SETX p.I2547T	FALS		[124]
TARDBP p.G287S	VAPB p.M170I	SALS		[124]
TARDBP p.N352S	ANG p.K17I	FALS/FTD	61	[113]
SOD1 p.A5V	DAO p.S345F	FALS		[124]
SOD1 p.P67A	SETX p.I2547T	FALS		[124]
SOD1 p.G93D	ANG p.R121C	SALS	72	[122]
FUS p.R485W	SETX p.I2547T	SALS		[124]
FUS p.R521C	ANG p.K17I	FALS	53	[113]
DCTN1 p.R1049Q	SETX p.S323N	SALS		[124]
DCTN1 p.T1249I	SETX p.M274V	SALS		[124]
TAF15 p.R408C	SETX p.I2547T + p.T14I	SALS		[124]
SETX p.C1554G	DCTN1 p.H1270Q + FIG4 p.M694V	SALS		[124]

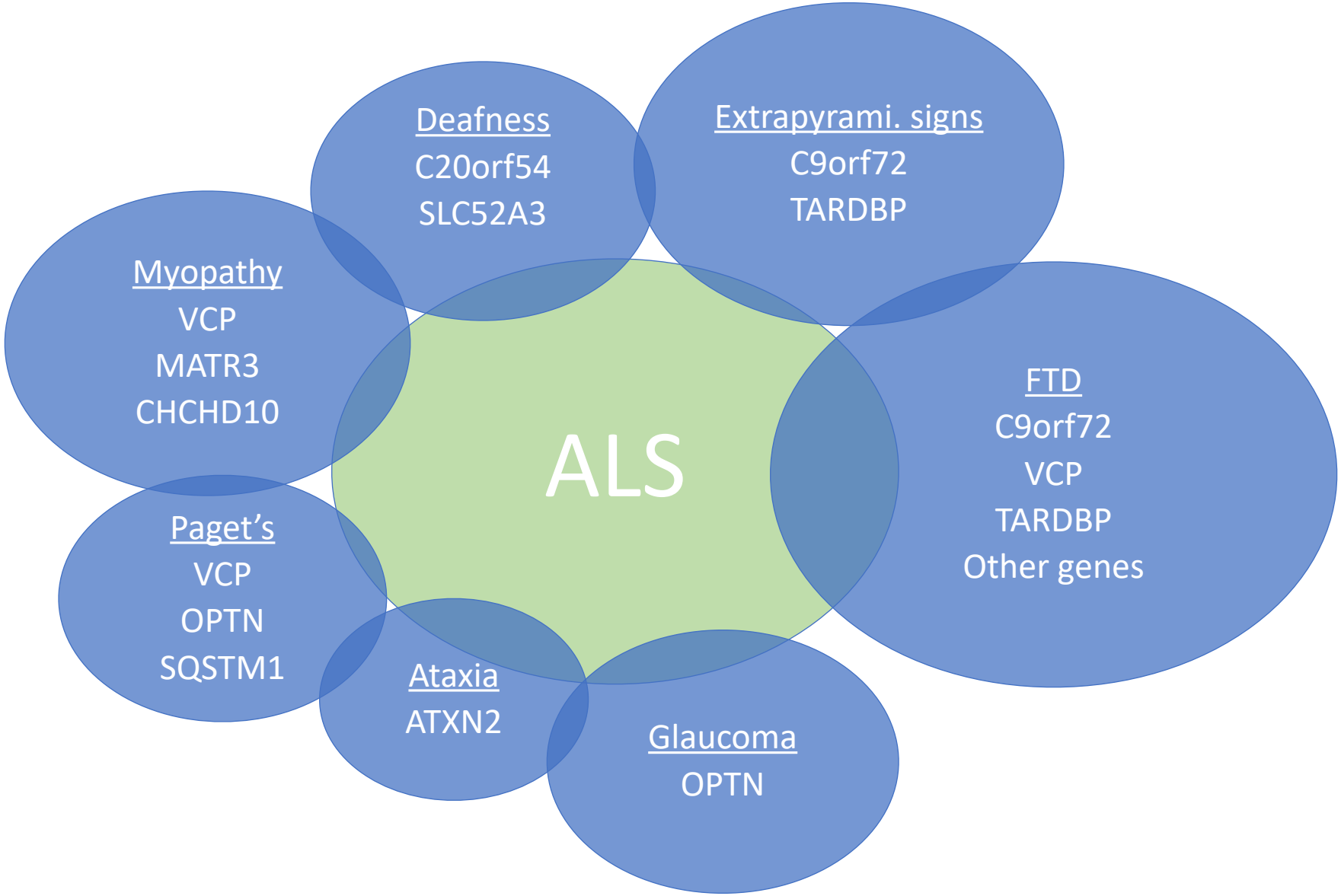
[a]Patients who carry combined mutations in causative genes of ALS/FTD support the notion of an oligogenic disease. The pathogenicity of several of these variants is unknown. Risk factors such as *ATXN2* intermediate repeats have been excluded from this list.

Lattante et al, Trends in Genetics 2015

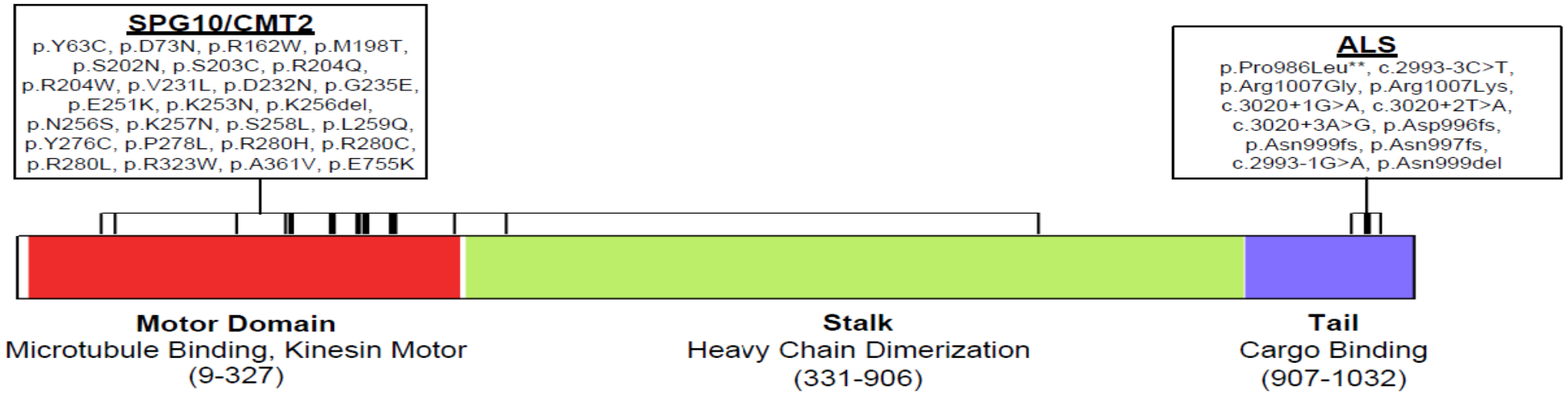
Of brain and bones

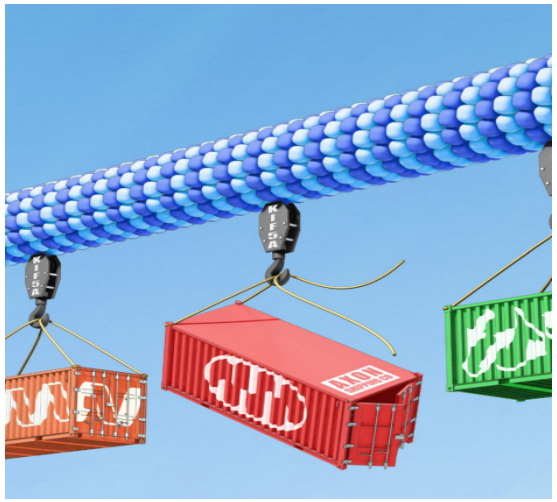
Il pleiotropismo dei geni della SLA

Pleitropismo dei geni della SLA



KIF5A
un gene tre fenotipi





Nicolas et al, Neuron 2018

Aggregati familiari di malattie psicotiche e suicidio

TABLE 5. Relatives of C9-Positive Cases and C9-Negative Cases Compared to Controls in a Cox Regression Proportional Model

Disease	Relatives	HR	95% CI	*p*
Parkinson disease	Relatives of C9-positive patients	1.3	0.5–3.7	0.570
	Relatives of C9-negative patients	0.7	0.4–1.1	0.126
Dementia	Relatives of C9-positive patients	1.6	1.1–2.4	0.017[a]
	Relatives of C9-negative patients	1.2	0.9–1.4	0.100
Depression	Relatives of C9-positive patients	3.3	1.6–7.0	0.002[a]
	Relatives of C9-negative patients	0.6	0.3–1.1	0.075
Schizophrenia/psychotic illness	Relatives of C9-positive patients	9.9	4.8–20.5	<0.0001[a]
	Relatives of C9-negative patients	3.9	2.4–6.5	<0.0001[a]
Suicide	Relatives of C9-positive patients	16.6	5.6–49.4	<0.0001[a]
	Relatives of C9-negative patients	5.1	2.2–12.1	<0.0001[a]

[a]Statistically significant.
CI = confidence interval; HR = hazard ratio.

Table 2. Prevalence and Relative Risk of Neuropsychiatric Conditions in First- and Second-Degree Relatives of Patients With ALS Compared With Controls

Condition	Relatives, No. Of Cases (n = 2116)	Relatives, No. Of Controls (n = 2139)	RR	*P* Value
Suicide	13	4	3.30	.04
Schizophrenia and psychotic illness	17	5	3.40	.02
Autism	10	1	10.10	.03
Depression	35	31	1.14	.59
Alcoholism	63	43	1.48	.045
Obsessive-compulsive disorder and rigid personality disorders	11	2	5.60	.02

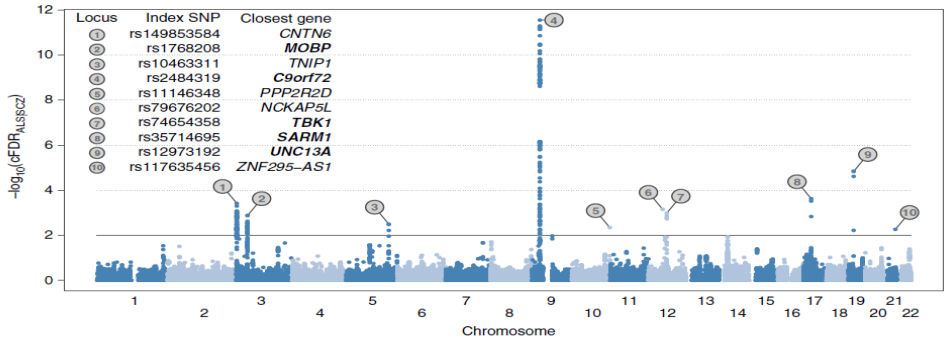


Figure 4 | Pleiotropy-informed ALS risk loci determined by analysis of cFDR in ALS GWAS *P*-values given schizophrenia GWAS *P*-values ($cFDR_{ALS|SCZ}$). Each point denotes a SNP; its *x* axis position corresponds to its chromosomal location and its height indicates the extent of association with ALS by cFDR analysis. The solid line indicates the threshold cFDR = 0.01. Any gene whose role in ALS is already established is in bold. A complete list of all loci at cFDR ≤ 0.05 is provided in Supplementary Table 8.

Correlazione genetica fra SLA e schizofrenia: 14,3% (7-22%)

Byrne et al, Ann Neurol 2013; O'Brien et al, JAMA Neurol 2018; McLaughin et al, Nature Comm 2017

I geni modificatori del fenotipo

Modificatori genetici del fenotipo della SLA

Table 2
Genes associated with low risk of ALS—susceptibility risk factor.

Locus	Chromosome	Gene ID	Gene name/function	Evidence	Inheritance	Mutation	Diagnosis	Onset	Positive replication studies	References
ALS9	14q11.1	*ANG*	Angiogenin/ribonuclease	Candidate gene association, Sanger	AD, sporadic	SNP, SNV	ALS, ALS-FTD, PD	Adult	Yes	(Greenway et al., 2004, 2006; van Es et al., 2011)
ALS11	6q21	*FIG. 4*	SAC1 lipid phosphatase domain containing (*S. cerevisiae*)/polyphosphoinositide phosphatase	Sanger	AD, sporadic	SNV	ALS, PLS, CMT	Adult	No	(Chow et al., 2009)
ALS13	12q24.12	*ATXN2*	Ataxin 2/unknown	Repeat association	Sporadic	CAG repeat	ALS, SCA2	Adult	Yes	(Elden et al., 2010)
	2p13.1	*DCTN1*	Dynactin/axonal transport	Sanger	AD	SNV	ALS	Adult	Yes	(Munch et al., 2004)
	3p11.2	*CHMP2B*	Chromatin modifying protein 2B/	Sanger	Sporadic	SNV	ALS, FTD	Adult	Yes	(Parkinson et al., 2006)
	7q36.2	*DPP6*	Dipeptidyl-peptidase 6/	GWAS	Sporadic	SNP	ALS	Adult	Yes	(Cronin et al., 2008a; van Es et al., 2008)
	6p21.1	*VEGF*	Vascular endothelial growth Factor/angiogenic, vascular, growth, migration & apoptosis factor	Gene association	Sporadic	SNP	ALS	Adult	No	(Lambrechts et al., 2003)
	19p13.12	*UNC13A*	Unc-13 homolog A/	GWAS	Sporadic	SNP	ALS	Adult	Yes	(Shatunov et al., 2010; van Es et al., 2009)
	22q12.1-q13.1	*NEFH*	Neurofilament, heavy polypeptide/intracellular transport to axons and dendrites	Sanger	Sporadic	SNV	ALS	Adult	No	(Al-Chalabi et al., 1999; Figlewicz et al., 1994)
	12q13.12	*PRPH*	Peripherin/cytoskeletal protein	Sanger	AD, sporadic	SNV	ALS	Adult	Yes	(Gros-Louis et al., 2004)
	5q35.3	*SQSTM1*	Sequestosome 1/scaffold protein, NFKB signaling pathway	Sanger	AD, sporadic	SNV	ALS	Adult	Yes	(Fecto et al., 2011)
	17q12	*TAF15*	TATA box binding protein (TBP)-associated factor/RNA polymerase II gene transcription	Sanger	AD	SNV	ALS	Adult	No	(Ticozzi et al., 2011)
	8p21.1	*ELP3*	Elongator acetyltransferase complex subunit 3/transcript elongation	Candidate gene association	Sporadic	SNP	ALS	Adult	No	(Simpson et al., 2009)
	5q13.2	*SMN1*	Survival of motor neuron 1	QPCR	AD, sporadic	CNV	ALS	Adult	Yes	(Corcia et al., 2002b)
	7q21.3	*PON1,2,3*	Paraoxonase/organophosphate hydrolysis	Candidate gene association	Sporadic	SNP, SNV	ALS	Adult	Yes	(Saeed et al., 2006)
	6p22.1	*HFE*	Hemochromatosis/iron absorption	Sanger	Sporadic	SNV	ALS	Adult	Yes	(Yen et al., 2004)
	1q24.2	*KIFAP3*	Kinesin-associated protein 3/small G protein	GWAS	Sporadic	SNP	ALS	Adult	No	(Landers et al., 2009)
	14q11.2	*APEX1*	APEX nuclease 1/apurinic/apyrimidinic endonuclease	Candidate gene Association	Sporadic	SNP	ALS	Adult	No	(Greenway et al., 2004)
	17q21.31	*PGRN*	Progranulin/cell growth regulator	Sanger	Sporadic	SNV	ALS, FTLD	Adult	No	(Schymick et al., 2007b)
	12p12.1-11.23	*ITPR2*	INOSITOL 1,4,5-trisphosphate receptor type 2	GWAS	Sporadic	SNV	ALS	Adult	No	(van Es et al., 2007)
	3p22.2	*PLCD1*	Phospholipase C delta 1	GWAS	Sporadic	SNV	ALS	Adult	No	(Staats et al., 2013)
	5q13.2	*ARHGEF28*	Rho guanine nucleotide exchange factor 28	Sanger	AD	SNV	ALS	Adult	No	(Droppelmann et al., 2013)

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; GWAS, genome wide association study; Q-PCR, quantitative-polymerase chain reaction; AD, autosomal dominant; autosomal recessive; SNV, single nucleotide variation; CNV, copy number variant; PLS, primary lateral sclerosis; PD, Parkinson disease; CMT, Charcot–Marie–Tooth disease; POAG, primary open-angle glaucoma; SCA2, spinocerebellar ataxia type 2.

Leblond et al, Exp Neurol 2014

Il polimorfismo CC del gene *UNC13A* modifica la sopravvivenza della SLA

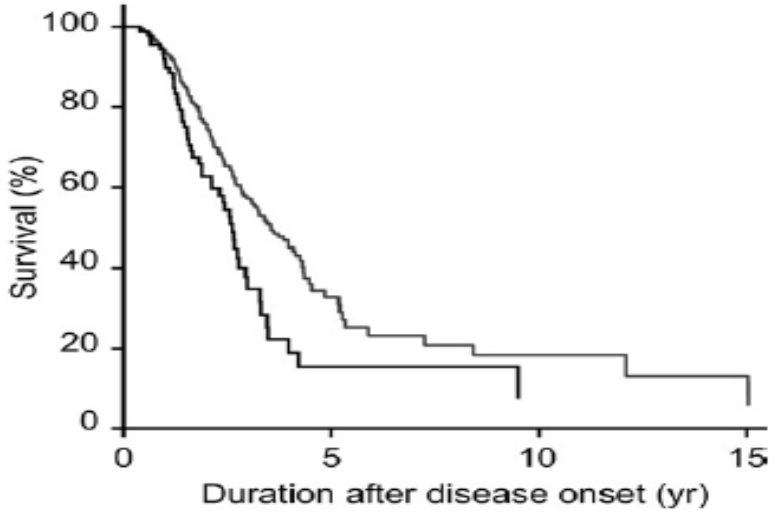


Fig. 1. Kaplan–Meier curves for rs12608932 genotypes according to a recessive genetic model in the population-based cohort. The black curve is for AA or AC genotypes, and the gray curve is for the CC genotype. C is the minor allele. The curves are adjusted for the covariates used in the survival analysis.

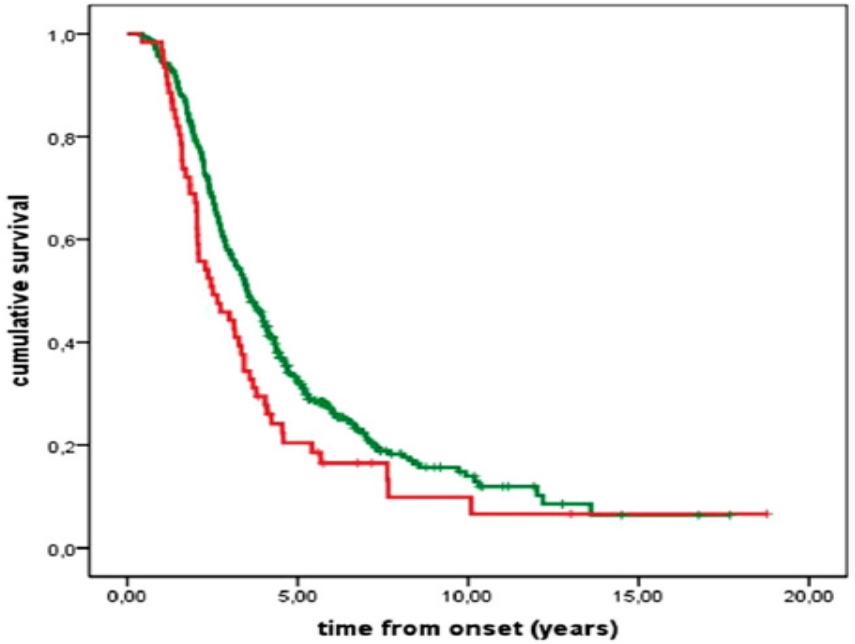


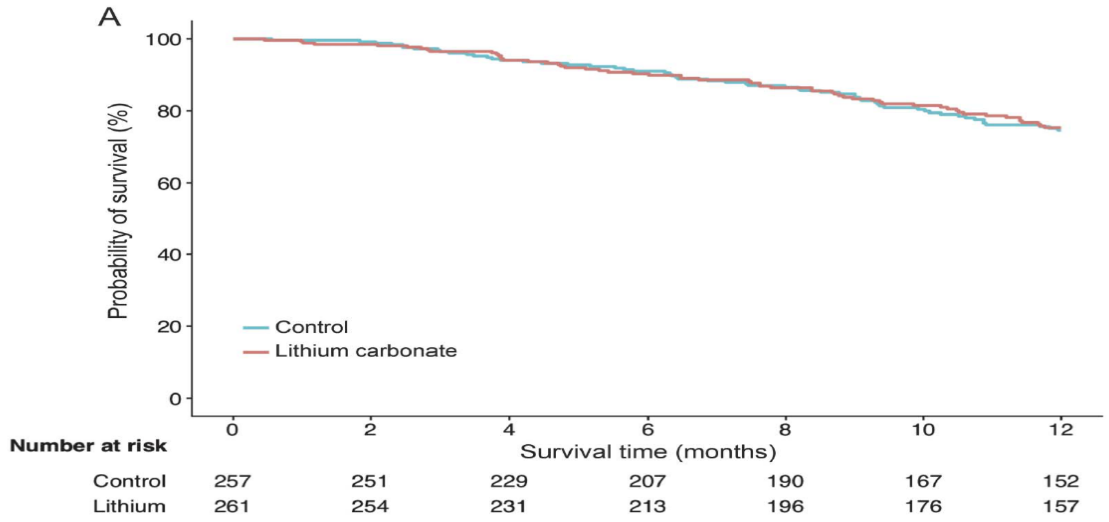
Fig. 1. Tracheostomy-free survival of patients according to a recessive model (AA/AC vs. CC). Green line = AA/AC; red line = CC. Ticks are censored patients.

I pazienti omozigoti per l'allele CC hanno una sopravvivenza inferiore di un anno rispetto ai pazienti con allele AA e AC

Diekstra et al, Neurobiol Aging 2012; Chiò et al Neurobiol Aging 2013

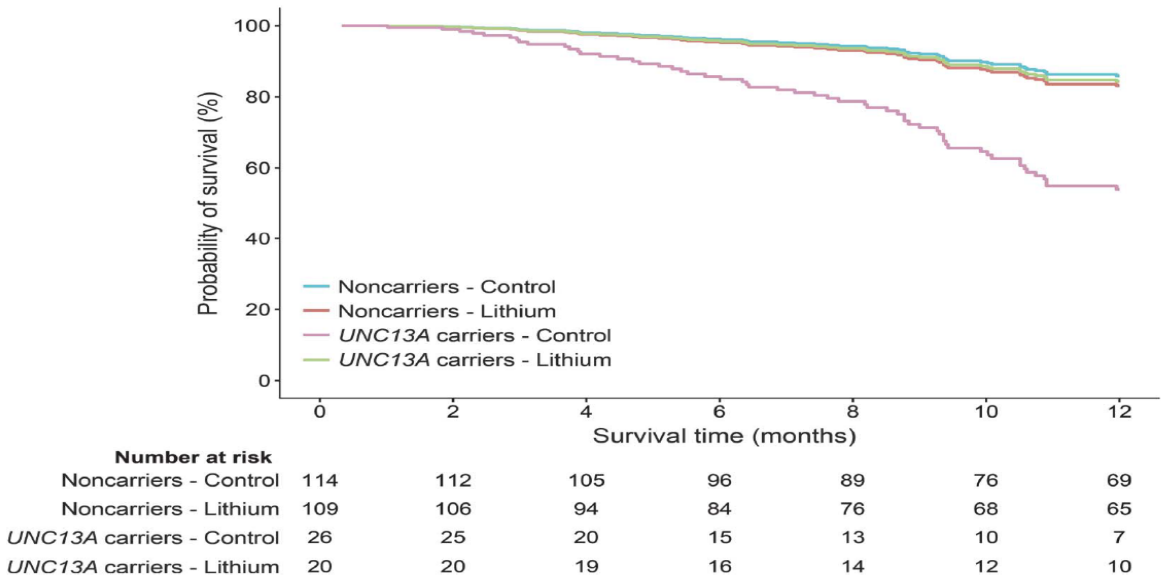
Il polimorfismo CC del gene *UNC13A* modifica la risposta alla terapia

Figure 1 Pooled analysis of treatment effect for lithium carbonate and 12-month survival for each genetic subgroup



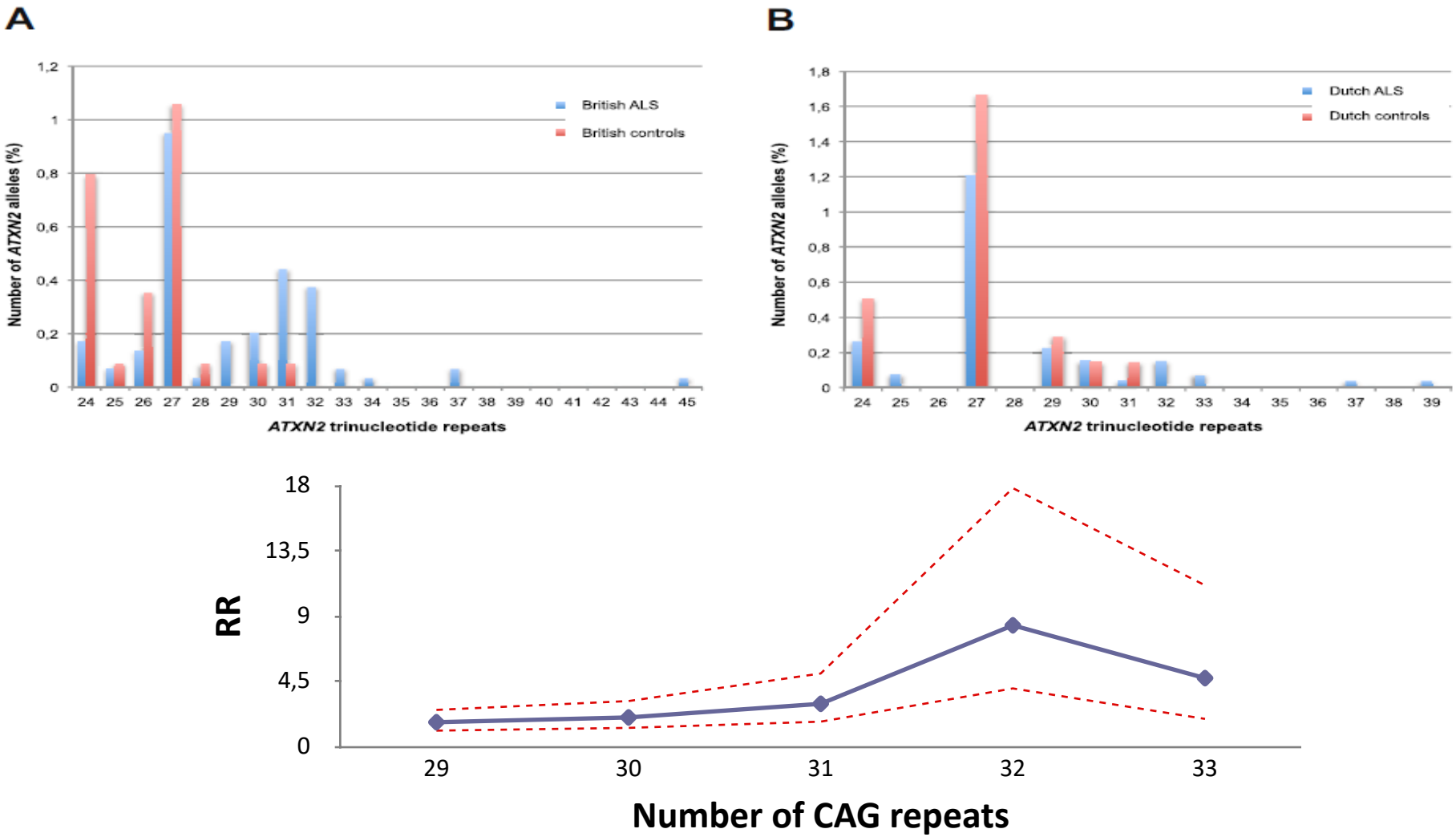
Metanalisi degli studi LitALS (Italia), LitRA (Paesi Bassi), e LiCALS (UK)

ıure 2 Cox proportional hazards model of 12-month survival and the interaction of lithium carbonate with *UNC13A* genotype



Van Eijk et al, Neurology 2017

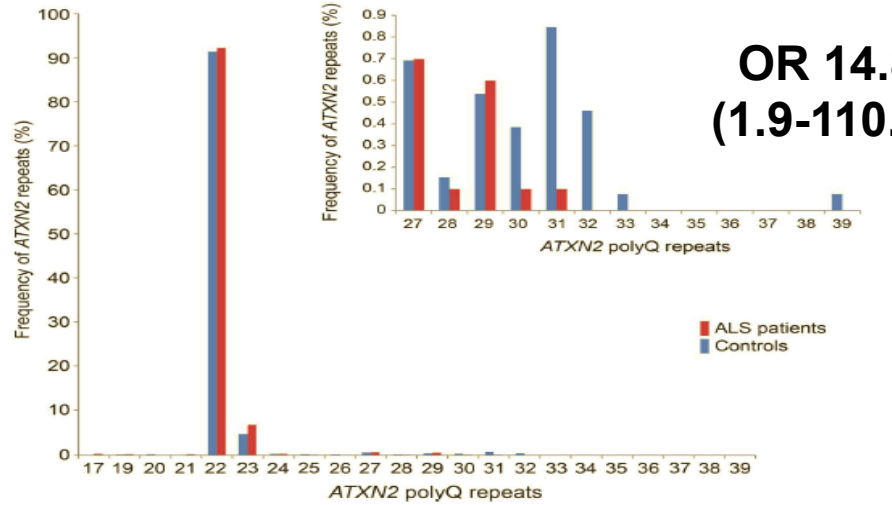
L’espansione intermedia del gene ATXN2 è un fattore di rischio per SLA



Sproviero et al, Neurobiol Aging 2017

L'espansione intermedia del gene ATXN2 è anche un modificatore del fenotipo

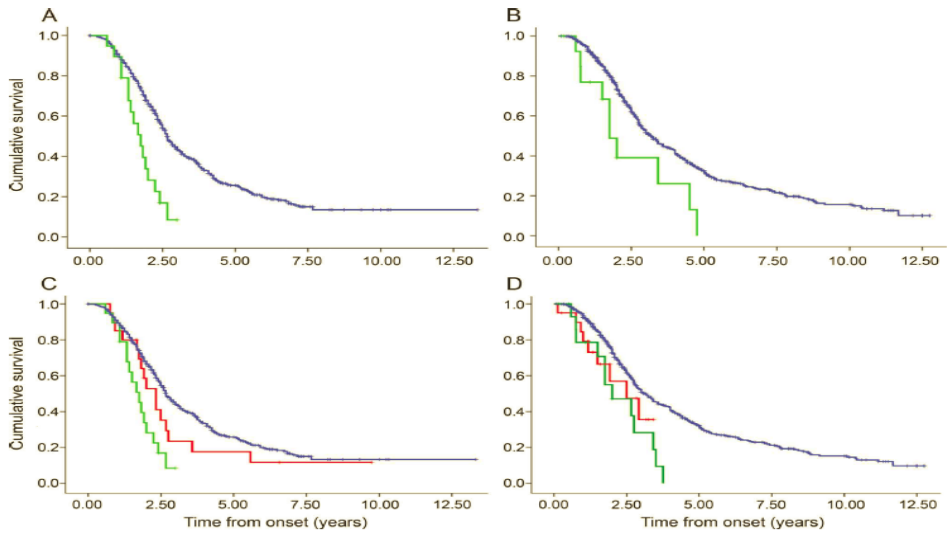
Figure 1 Discovery cohort



OR 14.8 (1.9-110.8)

The distribution of *ATXN2* polyQ repeat lengths in amyotrophic lateral sclerosis (ALS) and control cases. In the insert, data concerning cases and controls with ≥27 repeats are magnified. PolyQ lengths ≥31 are significantly more frequent in ALS cases ($p = 0.0001$) (blue, patients with ALS; red, controls).

Figure 2 Kaplan-Meier survival estimates from onset to death/tracheostomy



(A) Discovery cohort. Blue line, <31 polyQ repeats; green line, ≥31 polyQ repeats; $p = 0.0001$. (B) Validation cohort. Blue line, <31 polyQ repeats; green line, ≥31 polyQ repeats; $p = 0.009$. (C) Discovery cohort. Kaplan-Meier survival estimation from onset to death/tracheostomy. Blue line, <27 polyQ repeats; red line, 27-30 polyQ repeats; green line, ≥31 polyQ repeats; $p = 0.0001$. (D) Validation cohort. Kaplan-Meier survival estimation from onset to death/tracheostomy. Blue line, <27 polyQ repeats; red line, 27-30 polyQ repeats; green line, ≥31 polyQ repeats; $p = 0.003$.

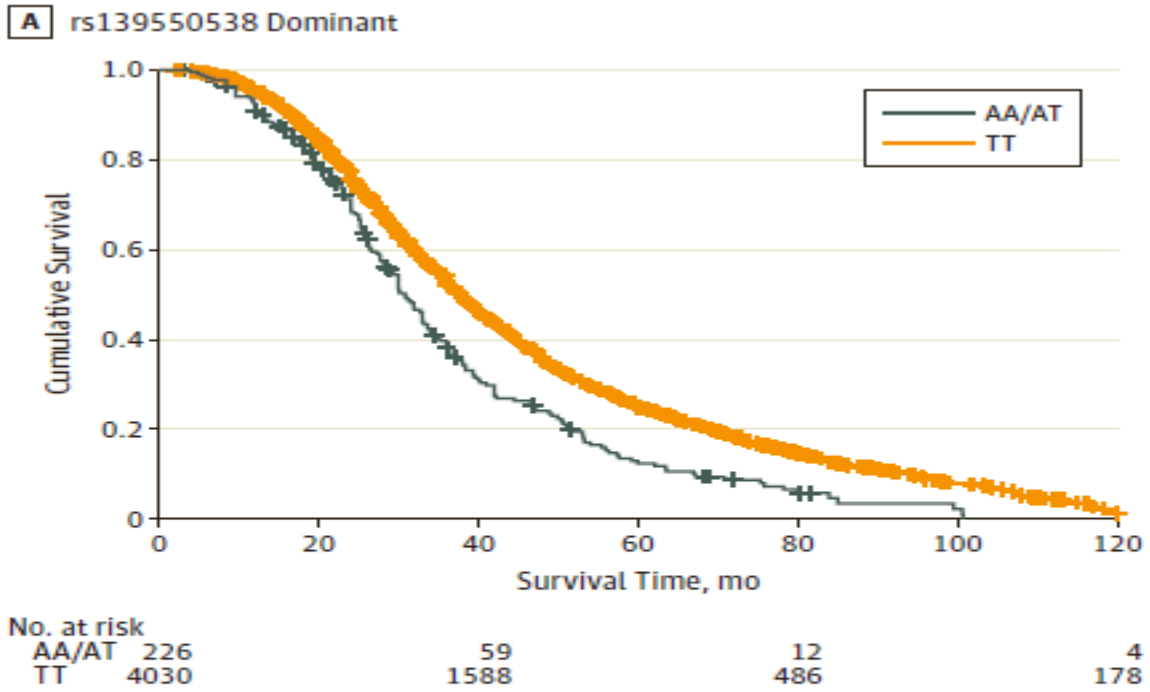
Table 1 Demographic and clinical characteristics of patients according to *ATXN2* repeat size

	Discovery cohort			Validation cohort		
Factor	<31 (n = 653)	≥31 (n = 19)	p	<31 (n = 645)	≥31 (n = 16)	p
Age at onset, y, mean (SD)	65.5 (10.8)	68.8 (8.1)	0.19	60.6 (12.1)	62.2 (10.4)	0.61
Female, n (%)	300 (45.9)	8 (42.1)	0.92	274 (42.5)	6 (37.5)	0.45
Bulbar onset, n (%)	217 (33.2)	1 (5.3)	0.005	167 (25.9)	2 (12.5)	0.18
Positive family history for ALS or FTD, n (%)	59 (9.0)	0	0.17	64 (9.9)	2 (12.5)	0.74

Abbreviations: ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia.

Chiò et al, Neurology 2015

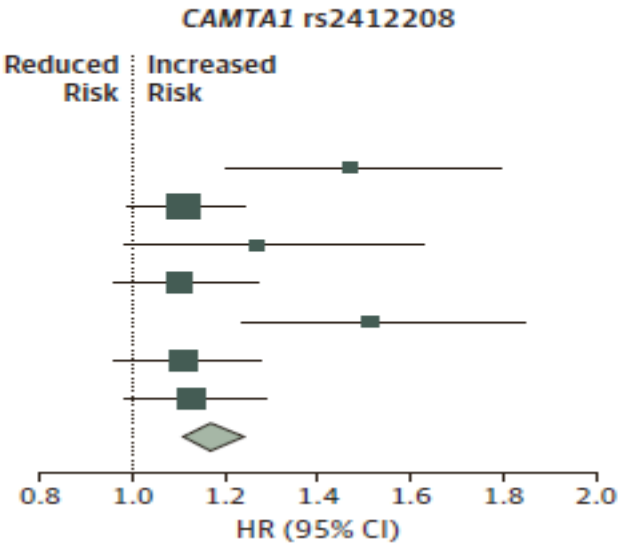
Il gene *CAMTA1* modifica la sopravvivenza



Allele	No. of Patients	No. of Events	No. (%) Censored	Survival, Median (95% CI), mo
AA/AT	226	187	39 (17.3)	30.8 (28.8-33.5)
TT	4030	2937	1092 (27.1)	36.7 (35.5-38.1)

Figure 3. Forest Plot of *CAMTA1* rs2412208 Hazard Ratio (HR) Estimates

Source	HR (95% CI)
GWAS Data Set	
UMC-1	1.46 (1.20-1.79)
UMC-2	1.10 (1.00-1.24)
Ireland	1.26 (1.00-1.61)
MGH-KCL-Evry	1.10 (1.04-1.26)
NIH-IT	1.51 (1.23-1.84)
SLAGEN	1.10 (1.01-1.28)
United Kingdom	1.10 (1.04-1.27)
Summary	1.17 (1.11-1.24)



Fogh et al, JAMA Neurology 2016

APOE E2 è un fattore di rischio per disturbi cognitivi nella SLA?

Table 1. Patients With ALS and Age- and Sex-Matched Population Control Individuals

APOE	No. (%) Patients With ALS (n = 357)	No. (%) Controls (n = 223)	*P* Value
Genotype			
ε2/ε2	2 (0.6)	0	.73
ε2/ε3	36 (10.1)	24 (10.8)	
ε3/ε3	275 (77.0)	169 (75.8)	
ε3/ε4	37 (10.4)	22 (9.9)	
ε2/ε4	6 (1.7)	7 (3.1)	
ε4/ε4	1 (0.3)	1 (0.4)	
Alleles[a]			
ε2	46 (6.4)	31 (7.0)	.85
ε3	623 (87.3)	384 (86.1)	
ε4	45 (6.3)	31 (7.0)	

Abbreviation: ALS, amyotrophic lateral sclerosis.

[a] Data were obtained for 714 patients with ALS and 446 controls.

Table 4. Multivariate Logistic Regression[a]

	Odds Ratio (95% CI)	*P* Value
Patients With ALS-FTD		
C9ORF72 vs non-*C9ORF72*	13.08 (4.75-36.02)	<.001
APOE		
ε2 vs non-ε2	2.61 (1.14-6.10)	.03
ε4 vs non-ε4	0.68 (0.25-1.85)	.46
Sex, female vs male	1.25 (0.63-2.48)	.53
Site of onset, bulbar vs spinal	1.97 (0.98-3.93)	.05
Age group, y		
≥70 vs <50	7.43 (1.61-34.71)	.01
60-69 vs <50	3.00 (0.64-14.04)	.16
50-59 vs <50	1.46 (0.29-7.28)	.64
Patients With ALS-Ci		
C9ORF72 vs non-*C9ORF72*	2.85 (1.11-7.31)	.03
APOE		
ε2 vs non-ε2	1.01 (0.45-2.20)	.99
ε4 vs non-ε4	0.68 (0.33-1.42)	.30
Sex, female vs male	1.27 (0.76-2.13)	.36
Site of onset, bulbar vs spinal	0.93 (0.54-1.61)	.80
Age group, y		
≥70 vs <50	2.88 (1.01-8.21)	.048
60-69 vs <50	2.85 (1.01-7.99)	.047
50-59 vs <50	1.74 (0.59-5.13)	.31

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-Ci, ALS with cognitive impairment; ALS-FTD, ALS with comorbid frontotemporal dementia.

[a] Data for patients with ALS with behavioral impairment are not reported because all values were nonsignificant.

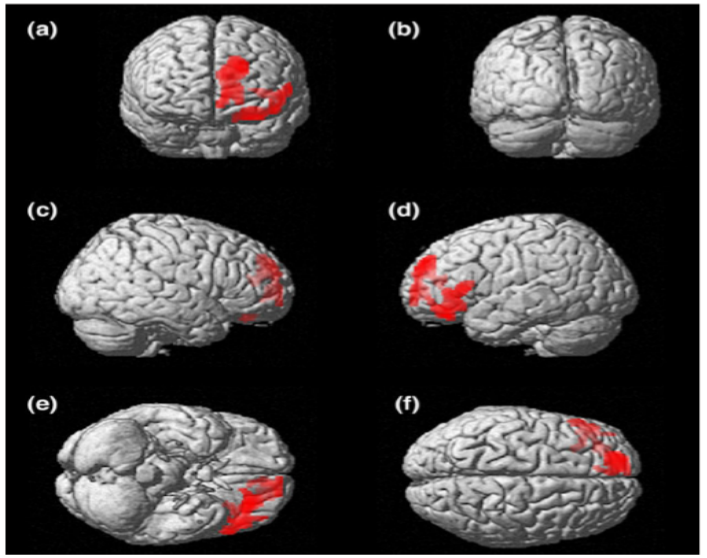


Figure 1 Glass brain rendering of multiple regression of *Apolipoprotein E* genotype, as transformed into rank variable, against whole brain metabolism. The clusters showing a statistically significant positive correlation are projected on brain surface. (a) Frontal view; (b) posterior view; (c) right view; (d) left view; (e) view from below; (f) view from above.

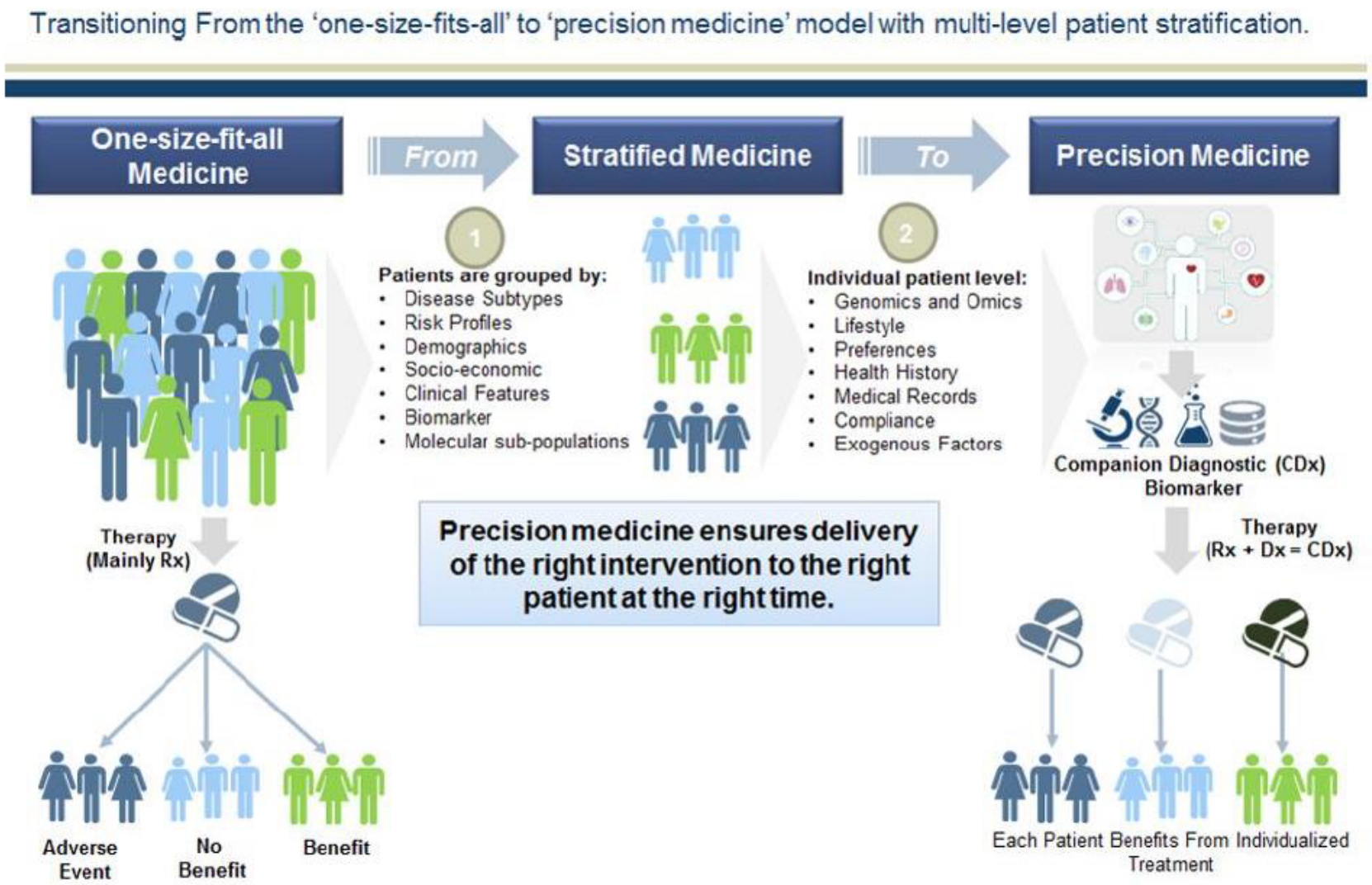
Table 2 Results of the positive correlation between whole brain metabolism and *Apolipoprotein E* genotypes

Cluster extent	*P* ($FDR_{corrected}$)	*Z*-score	Talairach coordinates			Lobe	Cortical region	BA
774	0.05	4.270	−20	56	25	Frontal	Left superior frontal gyrus	10
		3.087	−16	58	4	Frontal	Left medial frontal gyrus	10
		2.943	−8	41	9	Frontal	Left anterior cingulate	32
698	0.05	3.589	−30	36	−20	Frontal	Left middle frontal gyrus	11
		3.315	−48	32	−12	Frontal	Left inferior frontal gyrus	47
		3.286	−55	24	6	Frontal	Left inferior frontal gyrus	45

BA, Brodmann area.

Chiò et al, JAMA Neurol 2016; Canosa et al, Eur J Neurol 2019

ALS and Precision Medicine



What do we need for it?

1. Early diagnosis
2. Biomarkers
3. Progression prediction

CRESLA,Torino

Grazie

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