Les Régionales de la Santé

Maladies neurologiques dégénératives et traumatiques : mieux connaître pour mieux prendre en charge

Jeudi 14 décembre 2017, Paris

FILSLAN
Filière de Santé Maladies Rares Sclérose Latérale Amyotrophique et Maladies du Neurone Moteur

MAbImprove
LabEx Tours Montpellier

EURO NMD
Uniting bridges and breaking barriers in rare neuromuscular diseases

maladies rares

SLA: Une maladie? Un syndrome? L'hétérogénéité

CHRU
HÔPITAUX DE TOURS

Instituts thématiques

Inserm
Institut national de la santé et de la recherche médicale

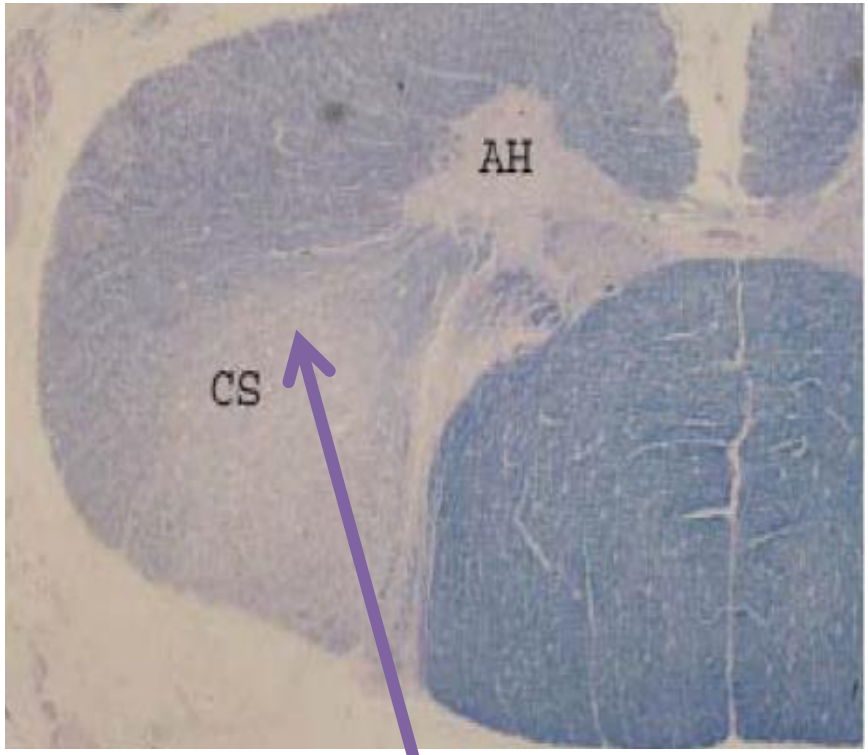
UNIVERSITÉ FRANÇOIS - RABELAIS TOURS

Définitions

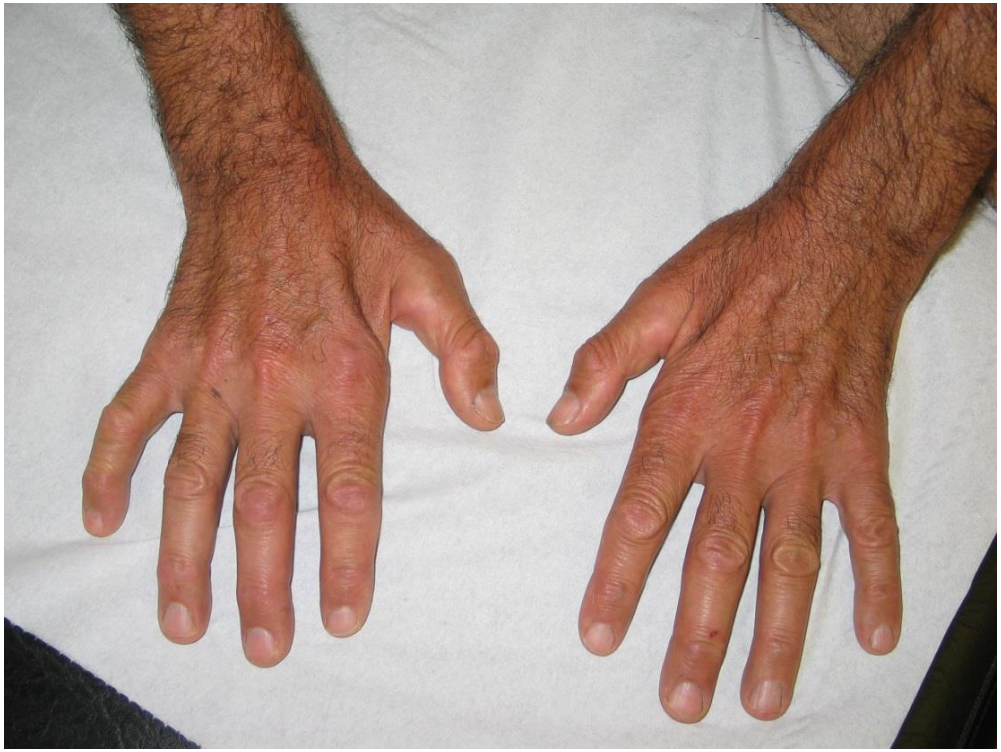
- *Maladie:*
  - *Pour l'OMS: Altération de l'état de santé.*
  - *Santé: Etat de complet bien-être physique, mental et social, et qui ne consiste pas seulement en une absence de maladie ou d'infirmité.*

- *Syndrome:*
  - *Ensemble de plusieurs symptômes ou signes en rapport avec un état pathologique donné et permettant, par leur groupement, d'orienter le diagnostic.*

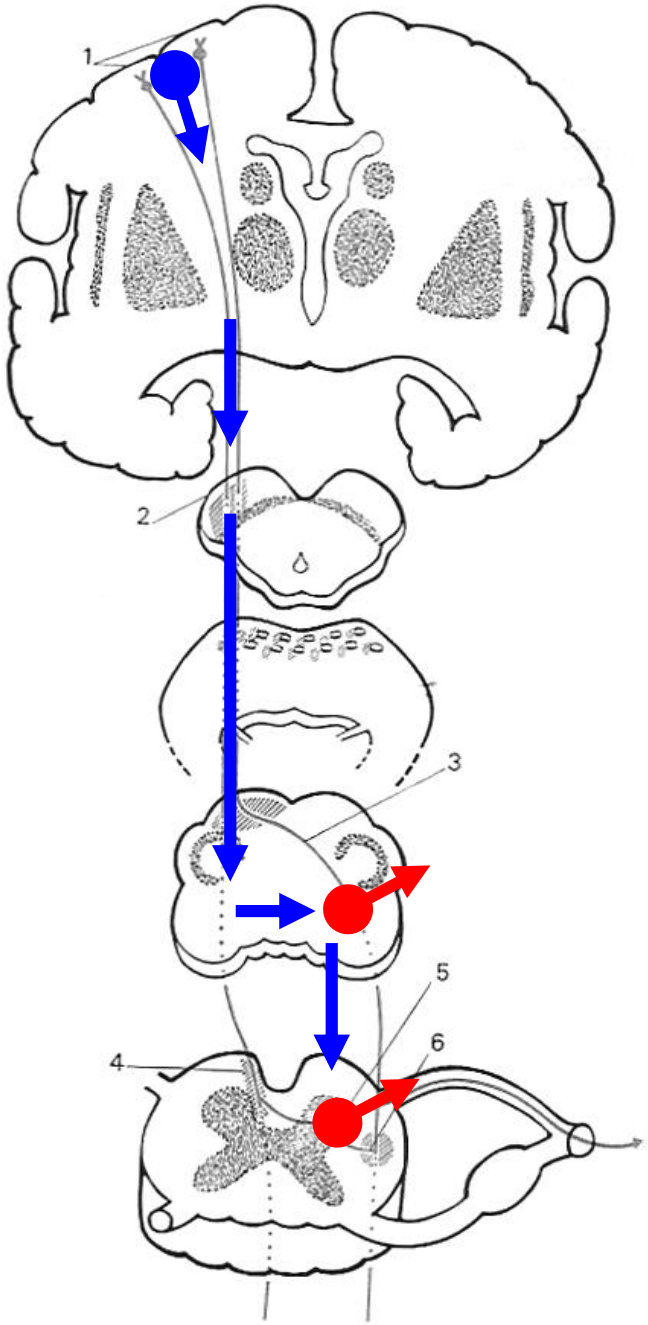
Sclérose Latérale Amyotrophique SLA
Maladie de Charcot



Sclérose du Faisceau cortico spinal

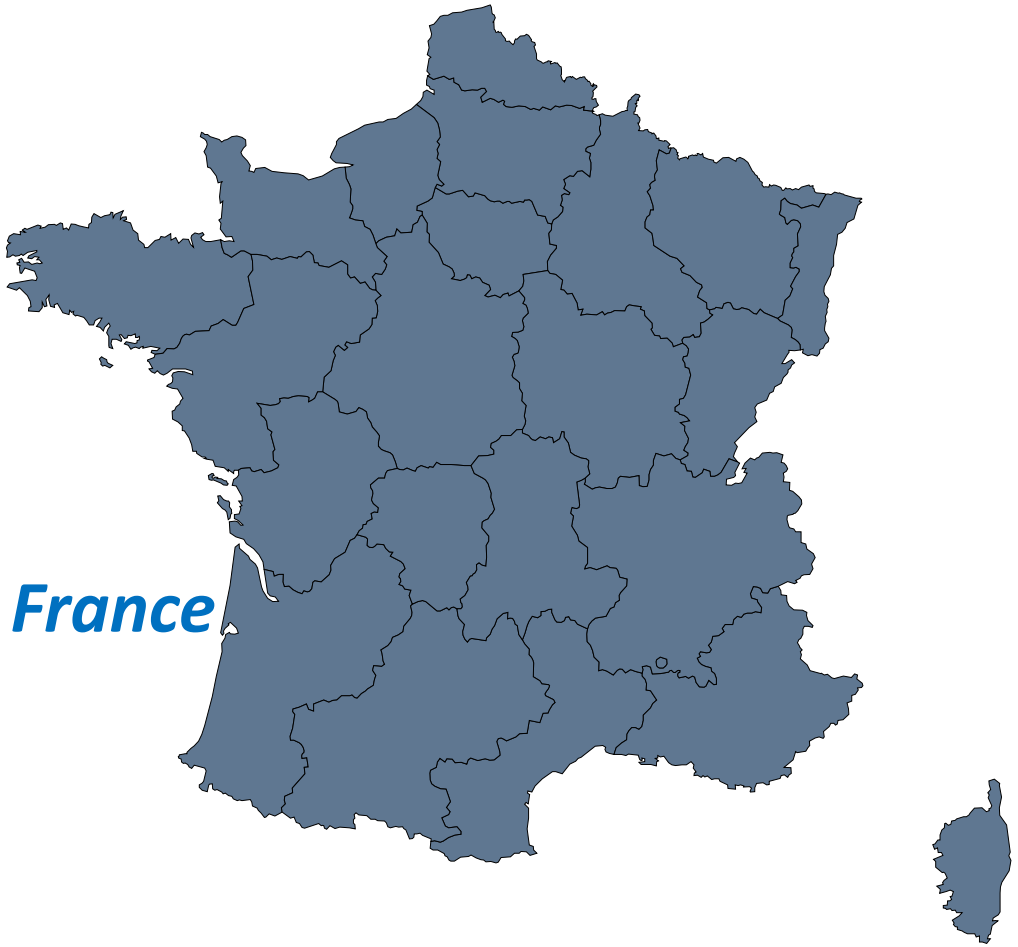


Amyotrophique


1
2
3
4
5
6

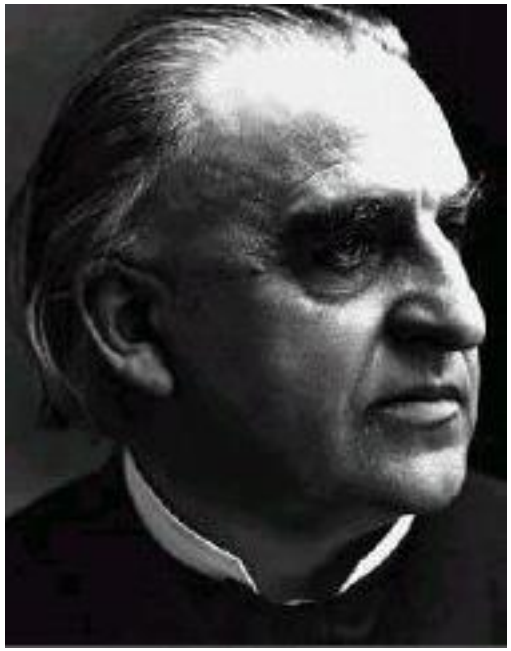
1 nouveau cas toutes les 6 heures en France

- Incidence de 2-5/100 000
- Prévalence: 5-7/100.000
- ***215.000 cas potentiels en France***



Comment apprend-on la SLA?

- *3 Hommes/ 2 Femmes.*
- *Forme bulbaire ou spinale.*
- *Forme Sporadique ou Familiale.*
- *Médiane de survie: 36 mois.*
- *Pas de traitement curatif.*

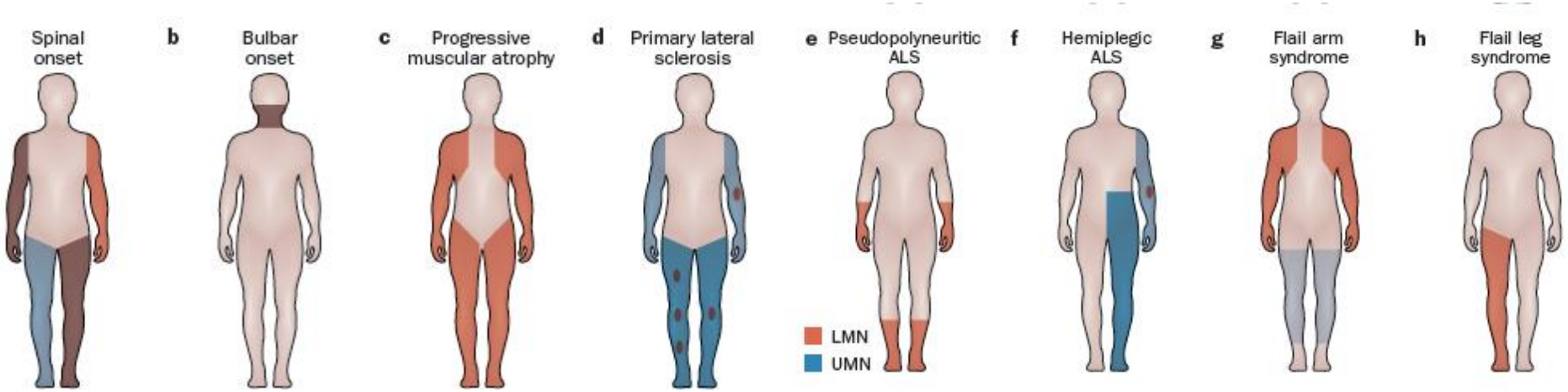


SLA: Une pathologie hétérogène

- Hétérogénéité clinique
- Hétérogénéité génétique
- Hétérogénéité neuropathologique
- Hétérogénéité physiopathologique

Hétérogénéité dans la présentation clinique

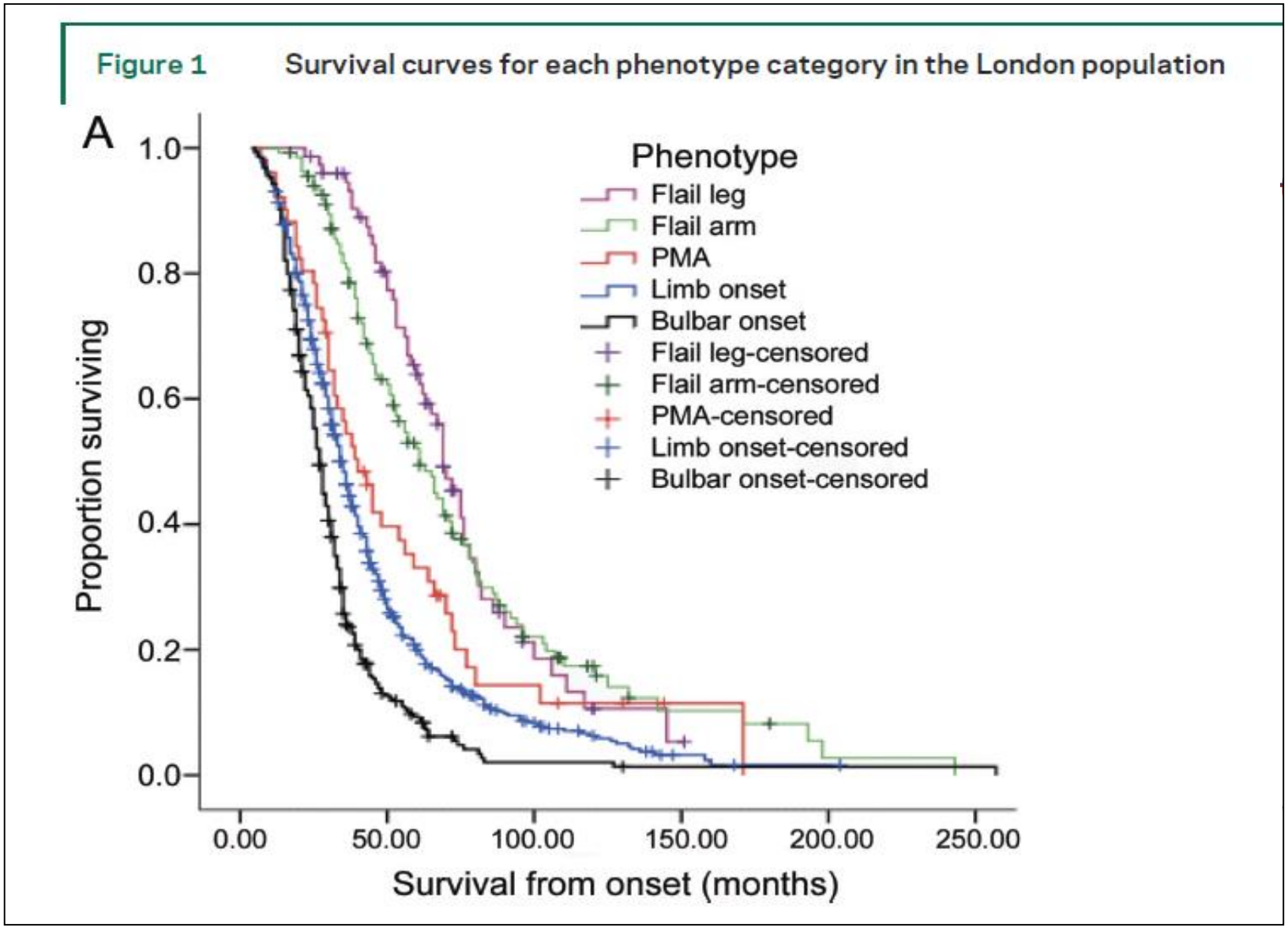
- *Age de début*
- *Prédominance ou non d'un motoneurone*



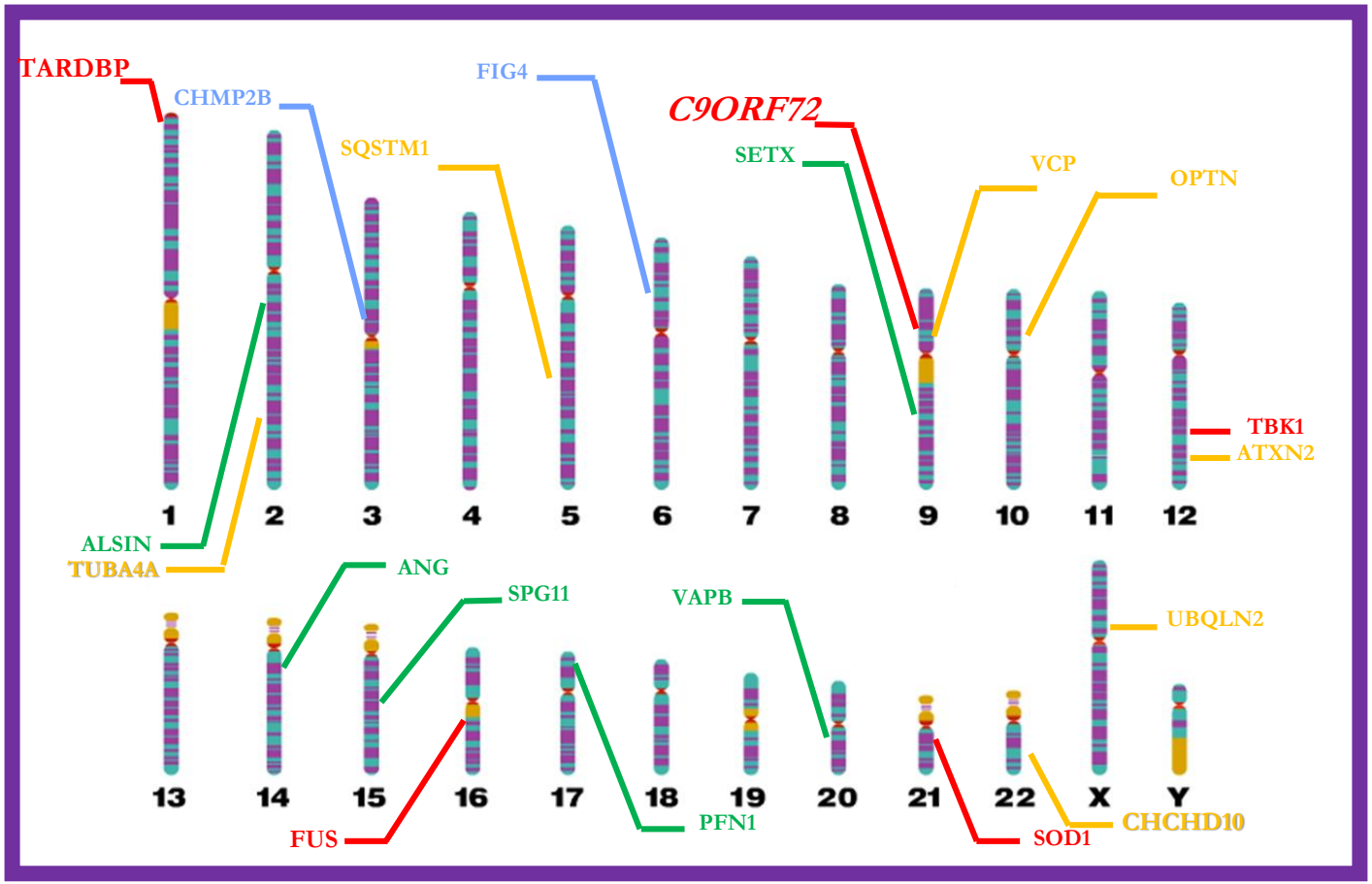
  - *Forme cachectique*
  - *Forme respiratoire*
  - *Troubles cognitifs*

nature REVIEWS NEUROLOGY

Hétérogénéité du profil évolutif



Hétérogénéité génétique de la SLA



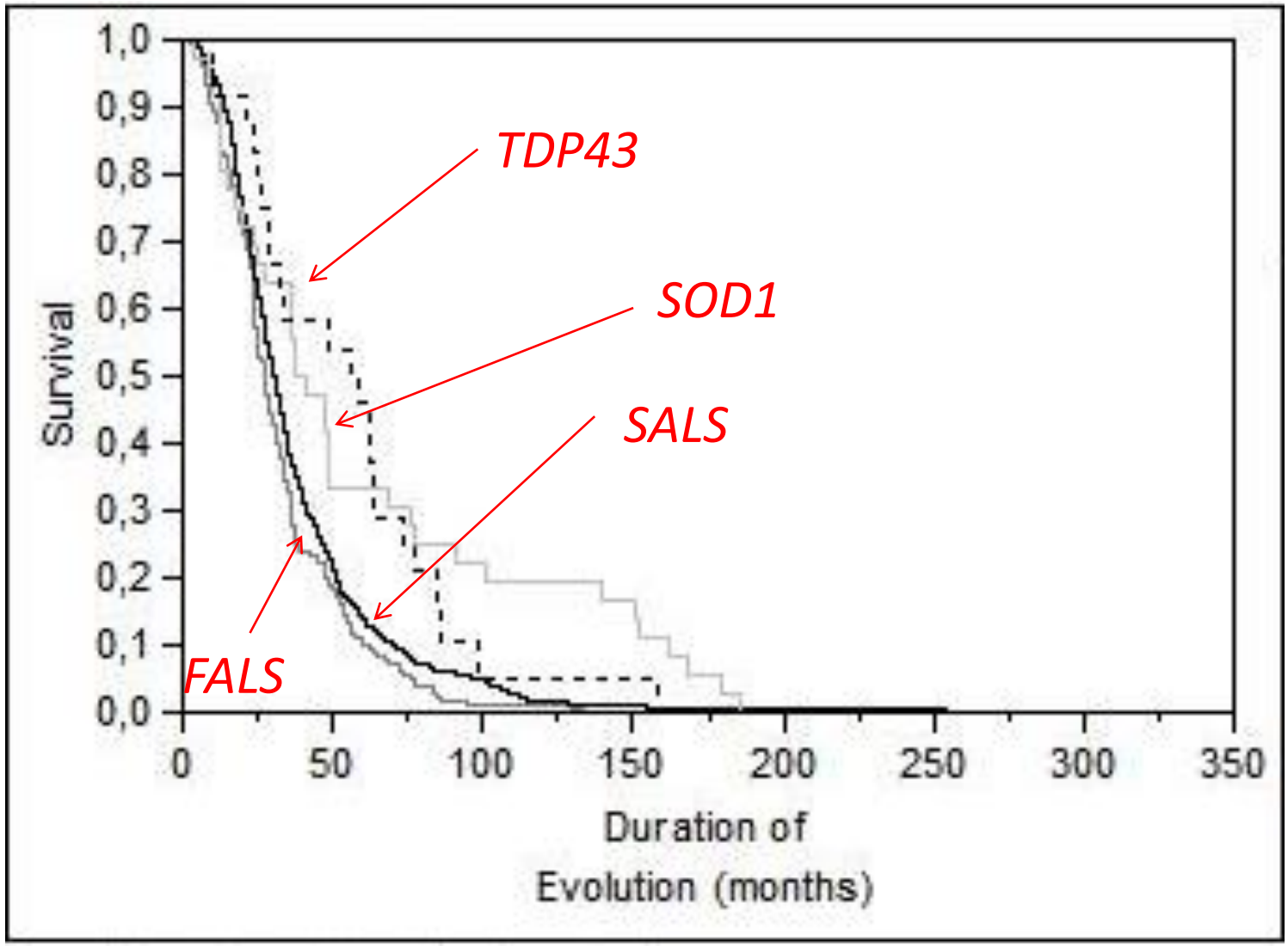
Red: ***Major Genes***

Green: ***Weak linkage***

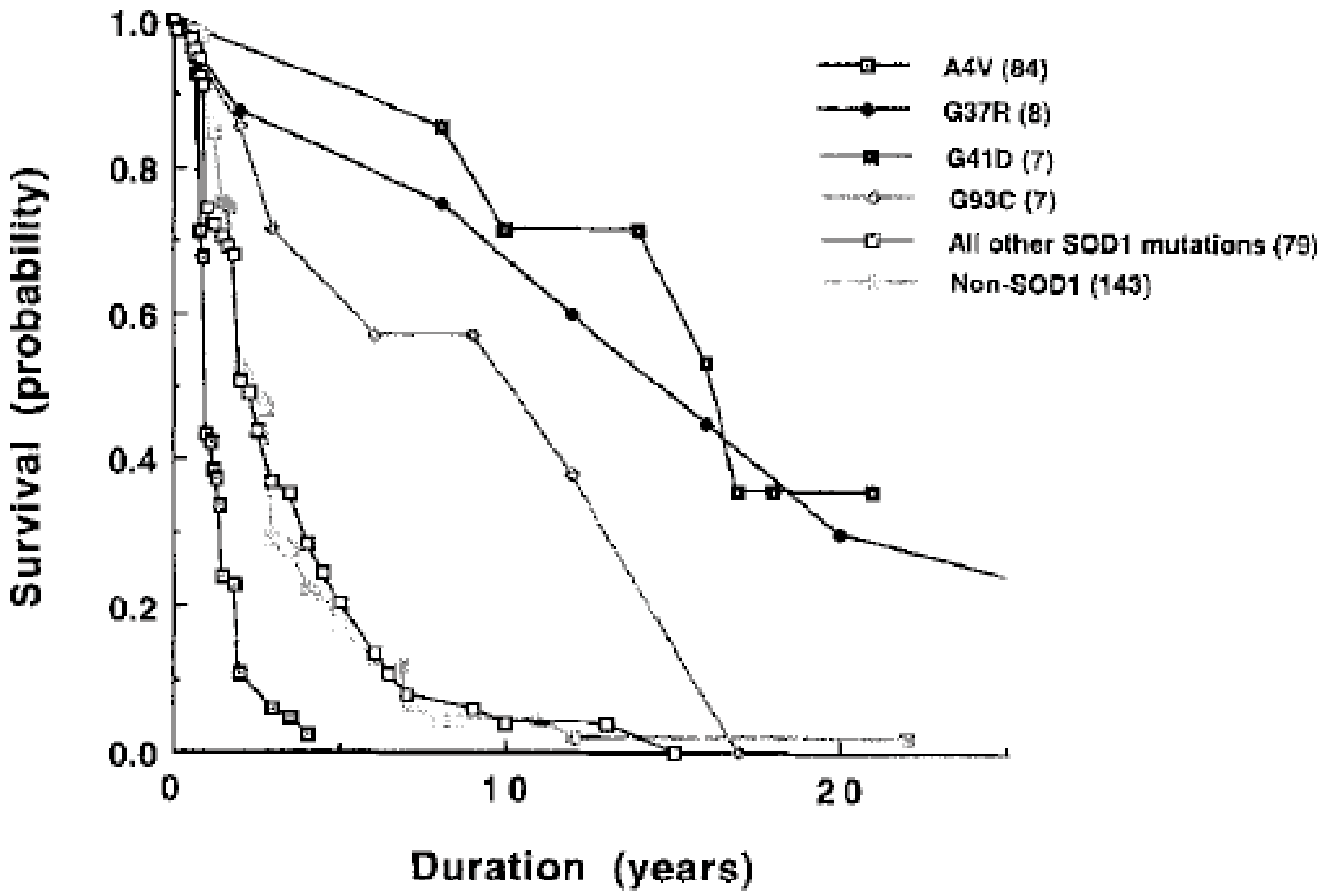
Orange: ***Need to be confirmed***

Blue: ***No conviction***

Profil évolutif variable selon le gène



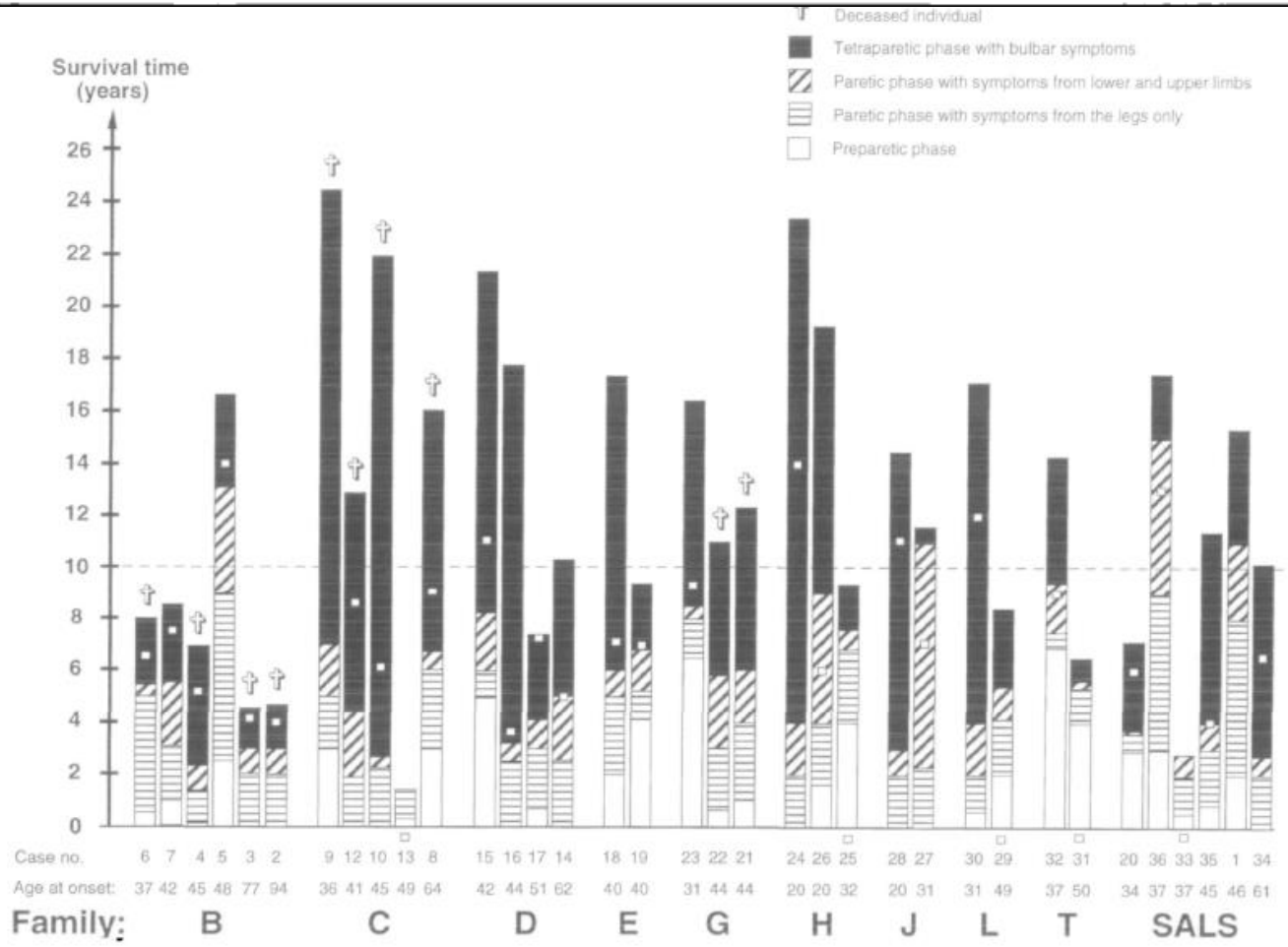
Profil évolutif modulé par la mutation



Brain (1996), **119**, 1153–1172

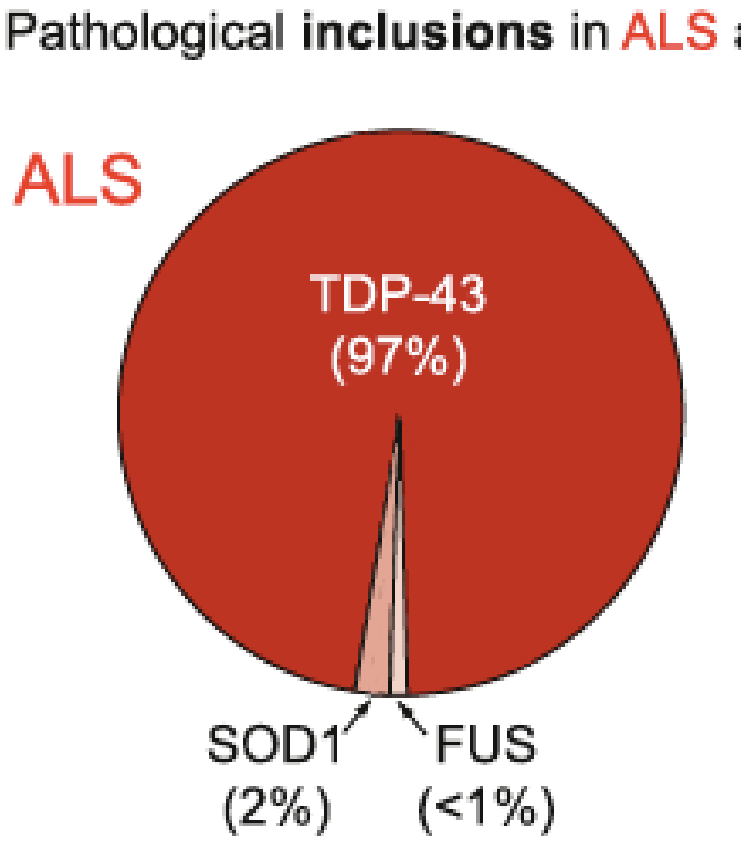
Autosomal recessive adult-onset amyotrophic lateral sclerosis associated with homozygosity for Asp90Ala CuZn-superoxide dismutase mutation

A clinical and genealogical study of 36 patients

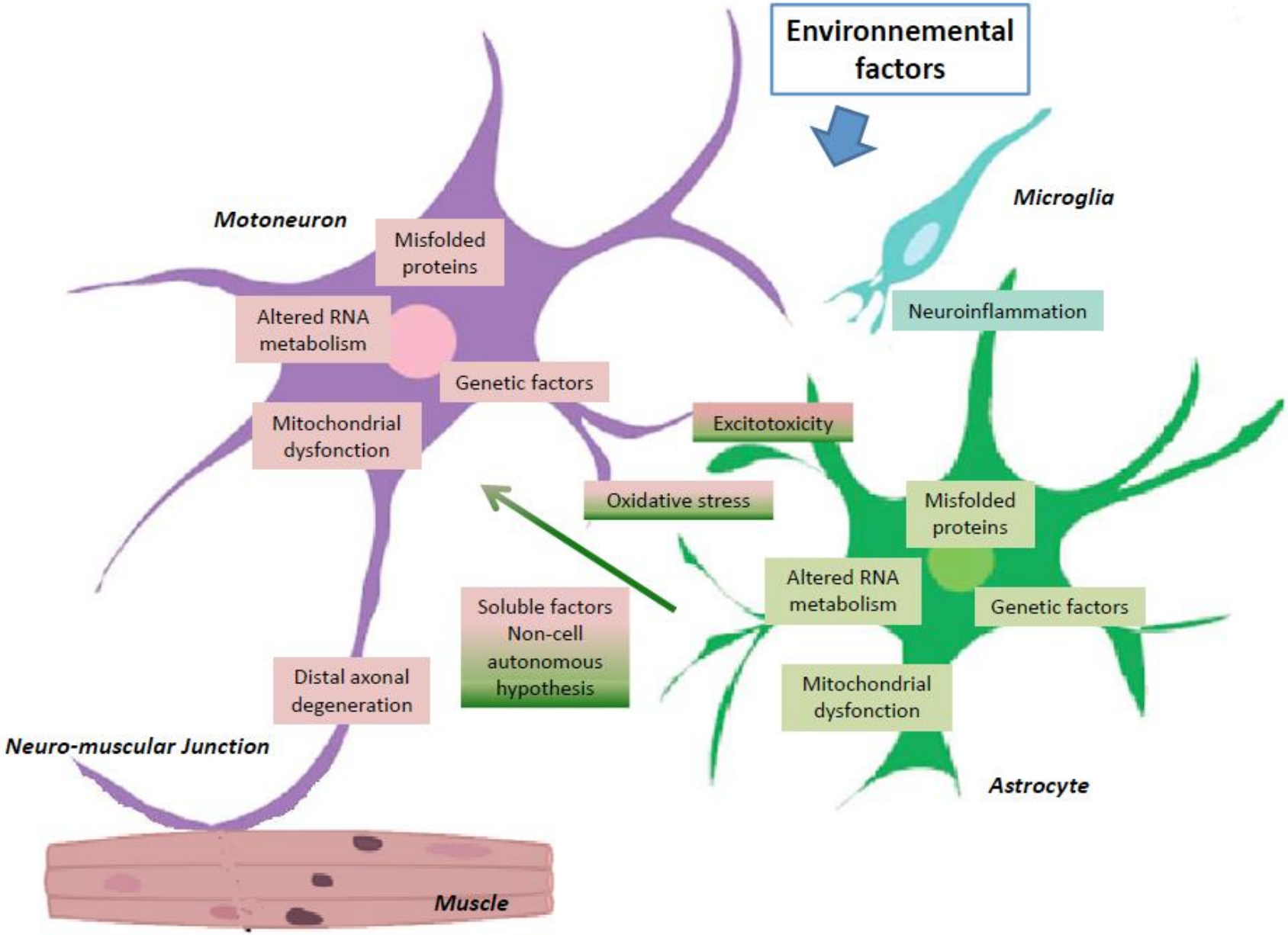


Hétérogénéité neuropathologique:

- SLA sporadiques:
- SLA familiales liées à une mutation:
  - TARDBP
  - c9ORF72
  - UBQLN2
  - OPTN
  - ANG
  - VCP



Hétérogénéité physiopathologique



Hétérogénéité physiopathologique

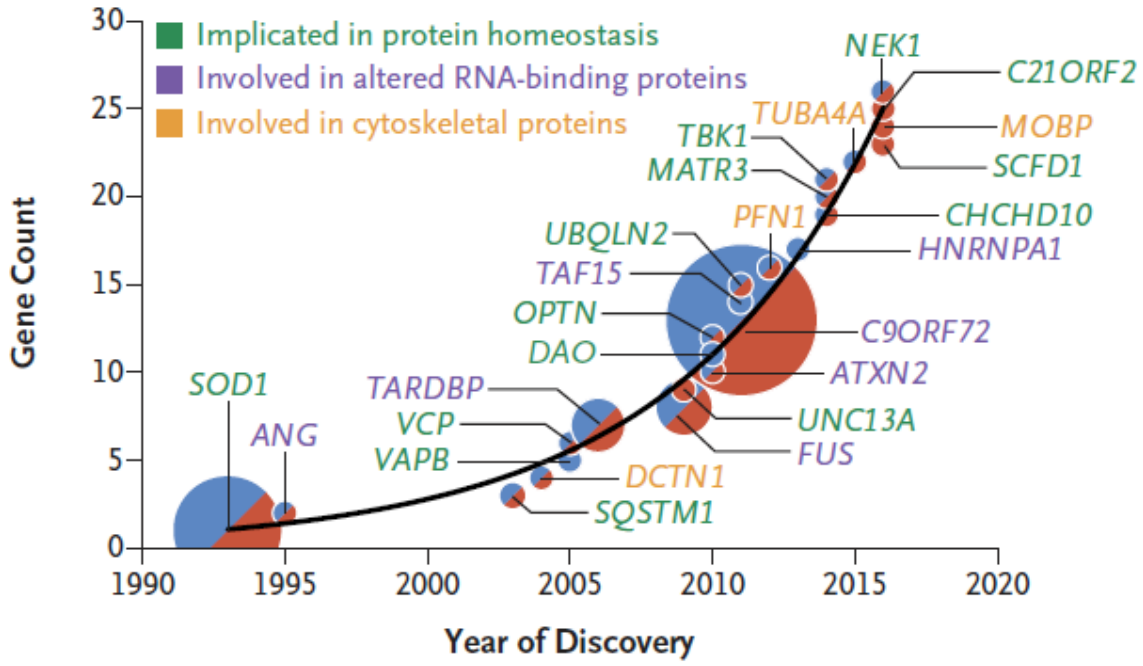
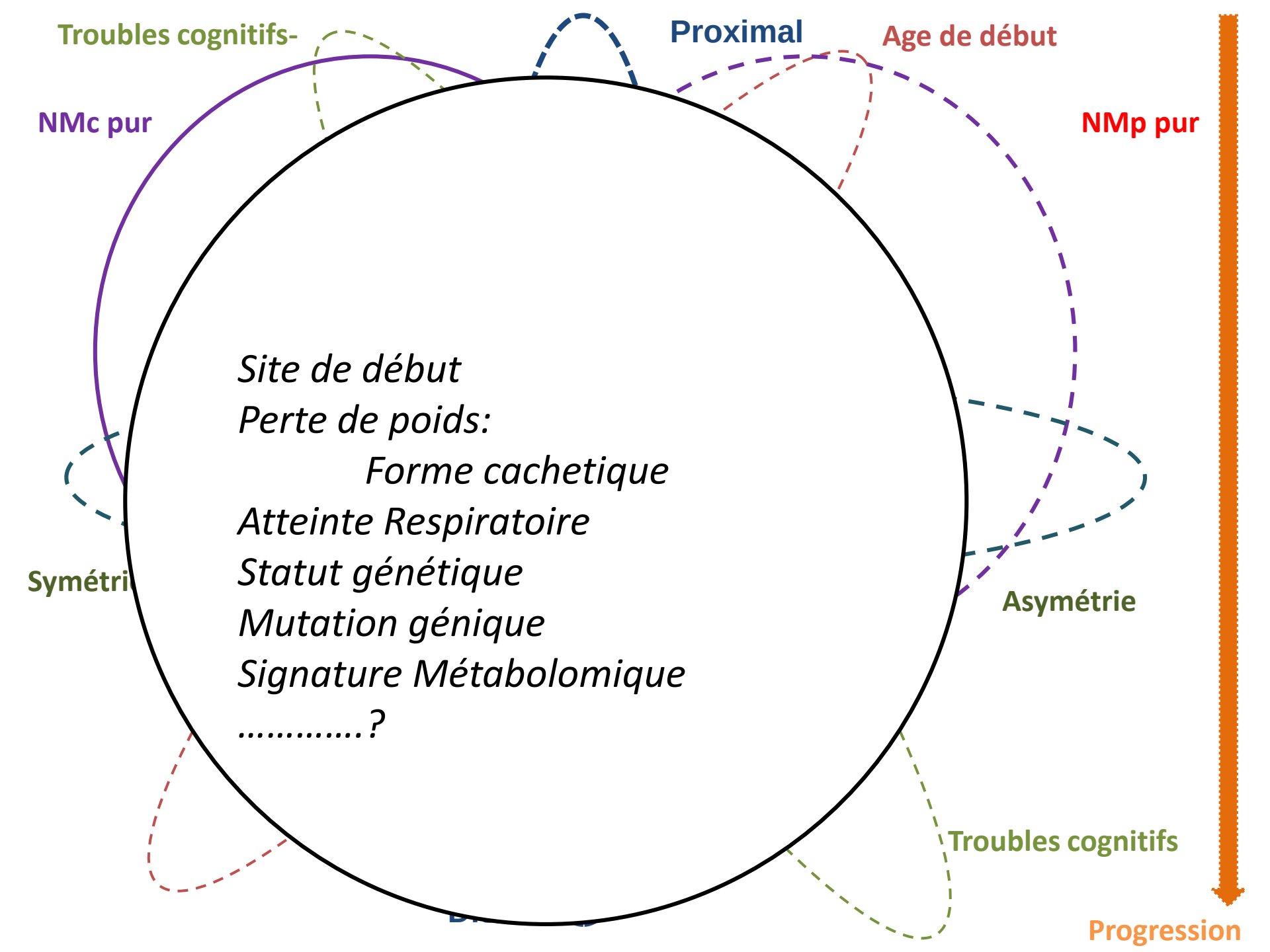


Figure 3. ALS Gene Discovery since 1990.

The cumulative numbers of known ALS genes have increased rapidly. The size of each circle reflects the proportion of all familial ALS cases associated with that gene (e.g., 20% for *SOD1* and 45% for *C9ORF72*). Blue circles indicate genes associated only with familial ALS, red circles indicate genes associated only with sporadic ALS, and circles that are half blue and half red indicate genes associated with both familial and sporadic ALS. Each of these genes has been found to be mutated in more than one ALS-affected family or in multiple, unrelated cases of sporadic ALS.


Troubles cognitifs-
Proximal
Age de début
NMc pur
NMp pur
Site de début
Perte de poids:
Forme cachetique
Atteinte Respiratoire
Statut génétique
Mutation génique
Signature Métabolomique
……?
Symétri
Asymétrie
Troubles cognitifs
Progression

SLA: Une maladie ou un syndrome?

Pourquoi cette question est cruciale?

Clinical trials in amyotrophic lateral sclerosis: why so many negative trials and how can trials be improved?

Hiroshi Mitsumoto, Benjamin R Brooks, Vincenzo Silani

	Rationale to proceed to RCT			Initiated by	Primary outcome	Study duration	Percentage of effect size	Number of patients	Riluzole use of all patients enrolled	Pharmacological assessment	Presumed biological target analysed	Discussion of negative results	Comments
	Hypothesis	SOD1 transgenic model	Early patient studies										
Xaliproden (2004)[22]	Neurotrophic factor	Others	Positive phase 2	Ind	Survival/VC <50%	18 months	38-34%	867 (study 1); 1210 (study 2)	none (study 1); 100% (study 2)	Insufficient	None	Yes, detailed	Large numbers of patients needed for positive results; drugs might affect survival and function differently
Creatinine (2004, 2008)[23,24]	Mitochondria	Yes	No	Inv	MVIC Slope	6 months; 9 months	50%; 15%	104; 107	No data	Only urine levels	None	Yes, detailed	Different phase 2 studies are needed
Vitamin E (2005)[25]	Oxidative stress	Yes	No*	Inv	Survival	18 months	50%	160	100%	Insufficient	None	Yes, detailed	More patients and longer duration studies are needed
Celecoxib (2006)[26]	Inflammation	Yes	No	Inv	MVIC slope	12 months	35%	200	69%	Yes	Yes, with CSF, PGE2	Yes, detailed	Detailed discussion on the rationale for the clinical trial
Pentoxifylline (2006)[27]	PDE4B-inhibitors and TNF-inhibitors	No animal tests	Off-label	Ind	Survival	18 months	N/A	400	100%	Insufficient	None	Yes, detailed	Survival worsened; drugs might affect survival and function differently
Minocycline (2007)[28]	Inflammation, apoptosis	Yes	Phase 2	Inv	ALSFRS-R slope	4 months lead-in; 9 months	18%	412	67%; 66%	None	None	Yes, detailed	No interaction with riluzole, but another study suggested adverse effects with riluzole[29]
TCH346 (2007)[30]	Apoptosis	Others	Phase 2	Ind	ALSFRS-R slope	16 week lead-in; 24 weeks	25%	591	86%	None	None	Yes, detailed	Several doses showed more deaths at higher doses
IGF-1 (2008)[31]	NTF	Others	2 RCTs	Inv	MMT	24 months	25%	330	70%	None	None	None	Trial done to settle previous conflicting results
CoQ10 (2009)[32]	Oxidative stress	Yes	Yes	Inv	Decreased on ALSFRS-R	9 months	20%	185	76%	Plasma levels	Planned but not pursued	None	Study showed futility to progress to a phase 3 study
Erythropoietin (2009)[33]	Neuroprotective	Yes†	Positive phase 2	Inv	Survival, Tracheostomy, or 23h-NIV	18 months; 12 months	N/A	208	100%	None	None	N/A	Phase 3 results available only as abstract
Glatiramer (2009)[34]	Inflammation	Yes, various	Phase 2	Ind	ALSFRS-R slope	>52 weeks	30%	366	100%	Discussed but not done	Mentioned but not pursued	None	Early immunological studies were done by others[35]
Lithium (2010-13)[36-40]	Autophagy	Yes‡	Yes‡	Inv	TTE; survival/LOA; ALSFRS-R; survival; survival	6 months; 15 months; 13 months; 16 months; 18 months	40%; 30%; 30%; 15%; 17·5%	88; 171; 107; 133; 214	100%; 100%; 65%; 100%; 100%	Plasma levels only	None	Reached futility; stopped; no placebo; reached endpoint; a standard full study	All studies done to confirm previously reported results[37]
Talampanel (2010)[41]	Excitotoxicity	Yes	Phase 2	Ind	ALSFRS-R change	12 months	20%	559	83%	Insufficient	None	None	Increased adverse effects; phase 3 results, available only as abstract

(Table 2 continues on next page)

	Rationale to proceed to RCT			Initiated by	Primary outcome	Study duration	Percentage of effect size	Number of patients	Riluzole use of all patients enrolled	Pharmacological assessment	Presumed biological target analysed	Discussion of negative results	Comments
	Hypothesis	SOD1 transgenic model	Early patient studies										
(Continued from previous page)													
Pioglitazone (2012)[42]	Peroxisome	Yes	No	Inv	Survival	18 months	18%	219	100%	None	None	Yes, detailed	None
Ceftriaxone (2013)[43]	Excitotoxicity	Yes; cell-based	Positive phase 2	Inv	Survival	>52 weeks	50%	513	50%	Yes	None	N/A	Phase 3 results; available only as abstract
Acetyl-L-Carnitine (2013)[44]	Mitochondria	Yes	No	Inv	Loss of self-sufficiency	12 months	30%	82	100%	None	None	Positive results for primary endpoint	Novel endpoint
Dexpramipexole (2013)[45]	Mitochondria	Yes	Other human; positive phase 2	Ind	Survival and ALSFRS-R§	12 months	37%	943	76%	PK levels; CSF	None	Yes, detailed	Challenges that concern interpretation of phase 2 study results; separate post-hoc analysis was done[46]
Olesoxime (2014)[47]	Mitochondria	Yes; cell-based	Phase 2	Ind	Survival	18 months	N/A	512	100%	Yes	None	Yes, detailed	Additional small phase 2 studies are needed

ALSFRS-R=amyotrophic lateral sclerosis functional rating scale-revised. CoQ10=coenzyme Q10. IGF-1=insulin-like growth factor 1. Ind=industry. Inv=investigators. LOA=loss of autonomy. MMT=manual muscle testing. MVIC=maximum voluntary isometric (muscle) contraction. NIV=noninvasive ventilation. N/A=not applicable. NTF=neurotrophic factors. Others=used other models (not SOD1). PDE4B=phosphodiesterase 4B. PGE2=prostaglandin E2. PK=pharmacokinetic. RCT=randomised controlled trial. SOD1=superoxide dismutase-1. TTE=time-to-event. TNF=tumour necrosis factor. VC=vital capacity. *No formal, previous human study, but there was an anecdotical report of a patient that vitamin E stabilised the disease. †Beneficial effects were only found in female mice. ‡Data source: Fornai and colleagues.[37] §Combined assessment of function and survival used.

Table 2: Large, multicentre, randomised clinical trials (RCTs) for disease-modifying drugs between 2004 and 2014

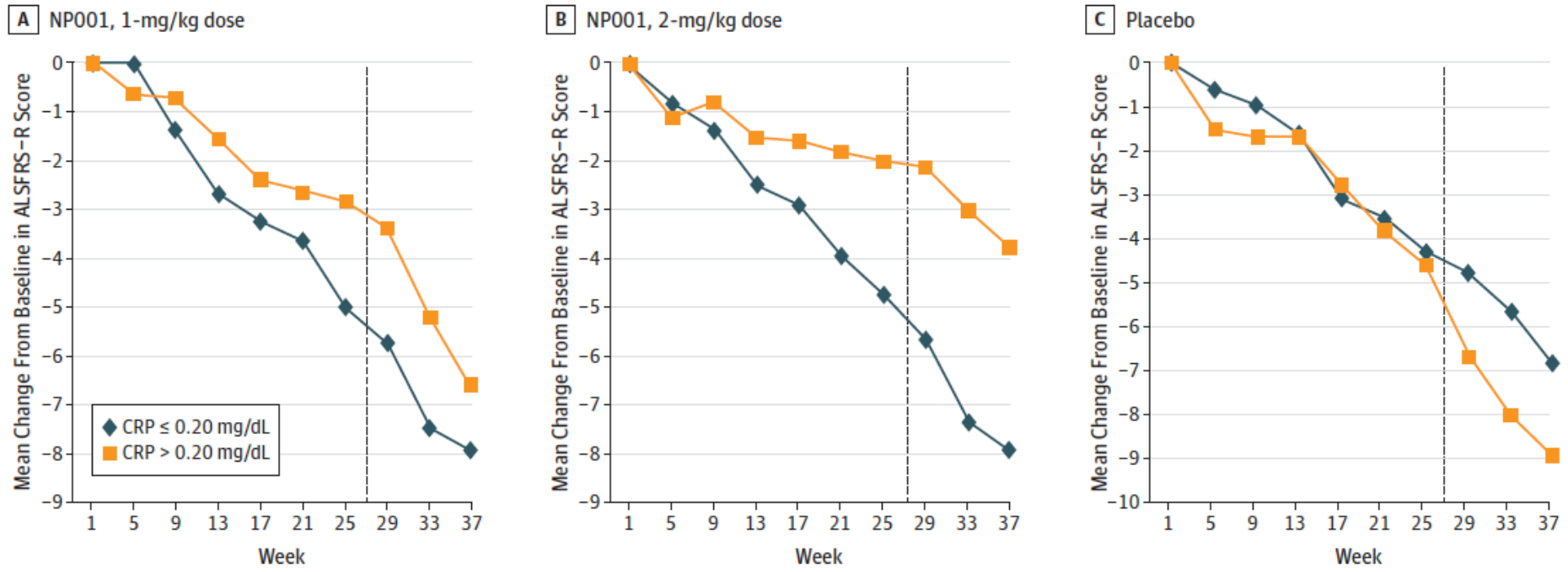
SLA: Un syndrome

- *Passer d'une prise en charge généraliste à une prise en charge personnalisée*

- *Nécessité de définir des groupes homogènes de patients SLA:*
  - *Paramètres restent à définir*

Traitement personnalisé?

Figure 3. Role of Serum C-Reactive Protein (CRP) Levels as Therapeutic Biomarker



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