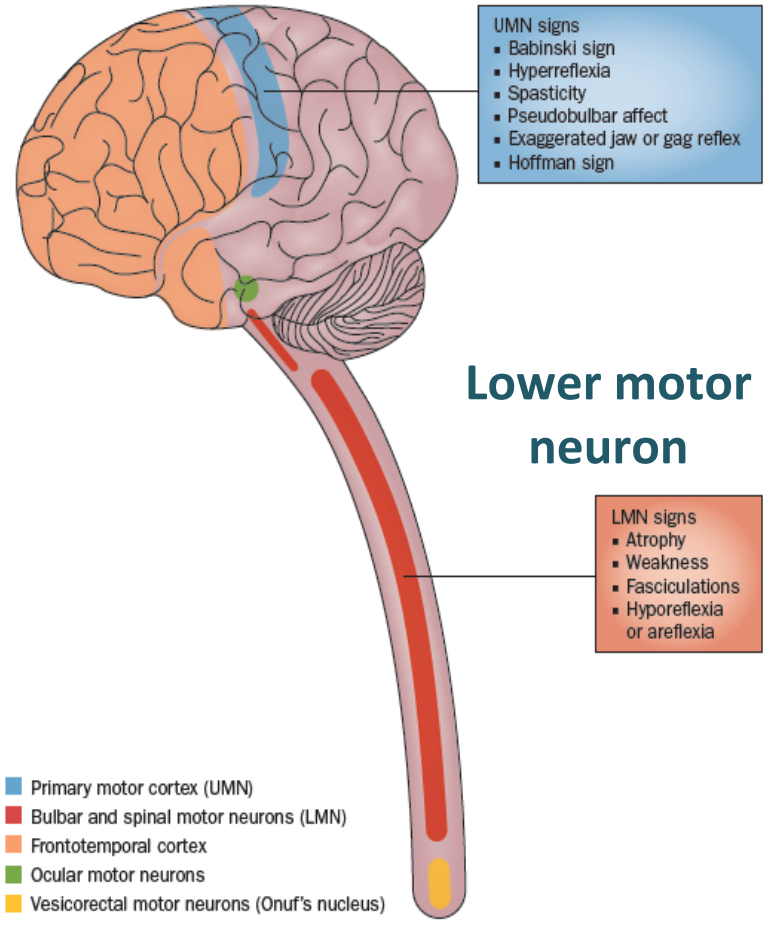
Corrélations Génotype-Phénotype de la SLA

P Couratier -Limoges

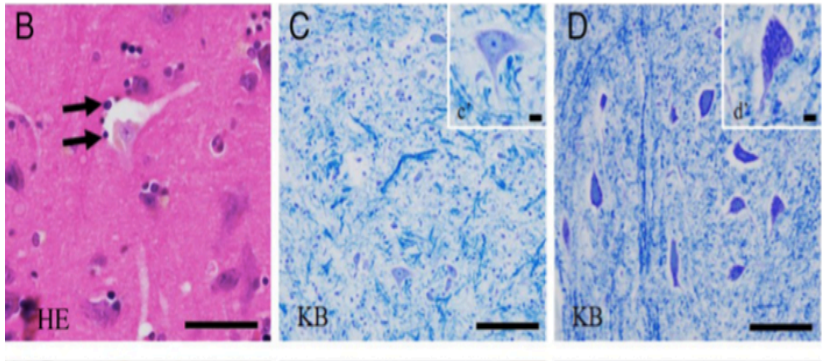
FILSLAN
Filière de Santé Maladies Rares
Sclérose Latérale Amyotrophique
et Maladies du Neurone Moteur

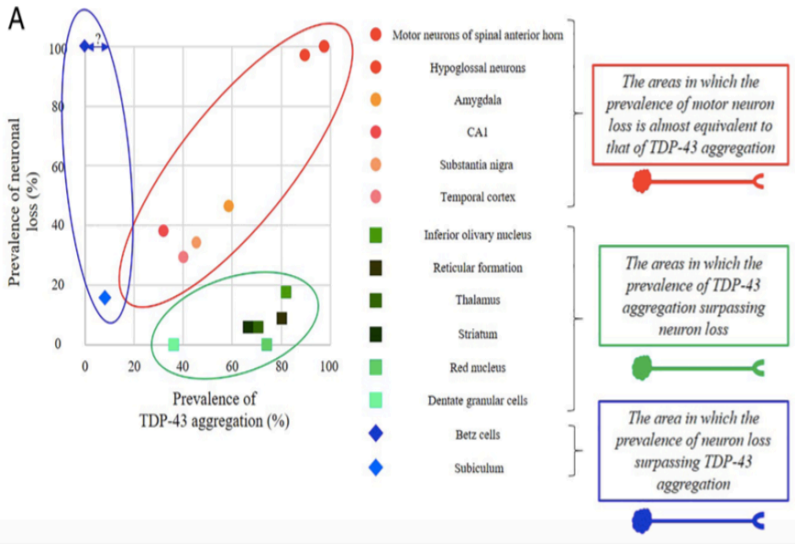
La SLA

Upper motor neuron

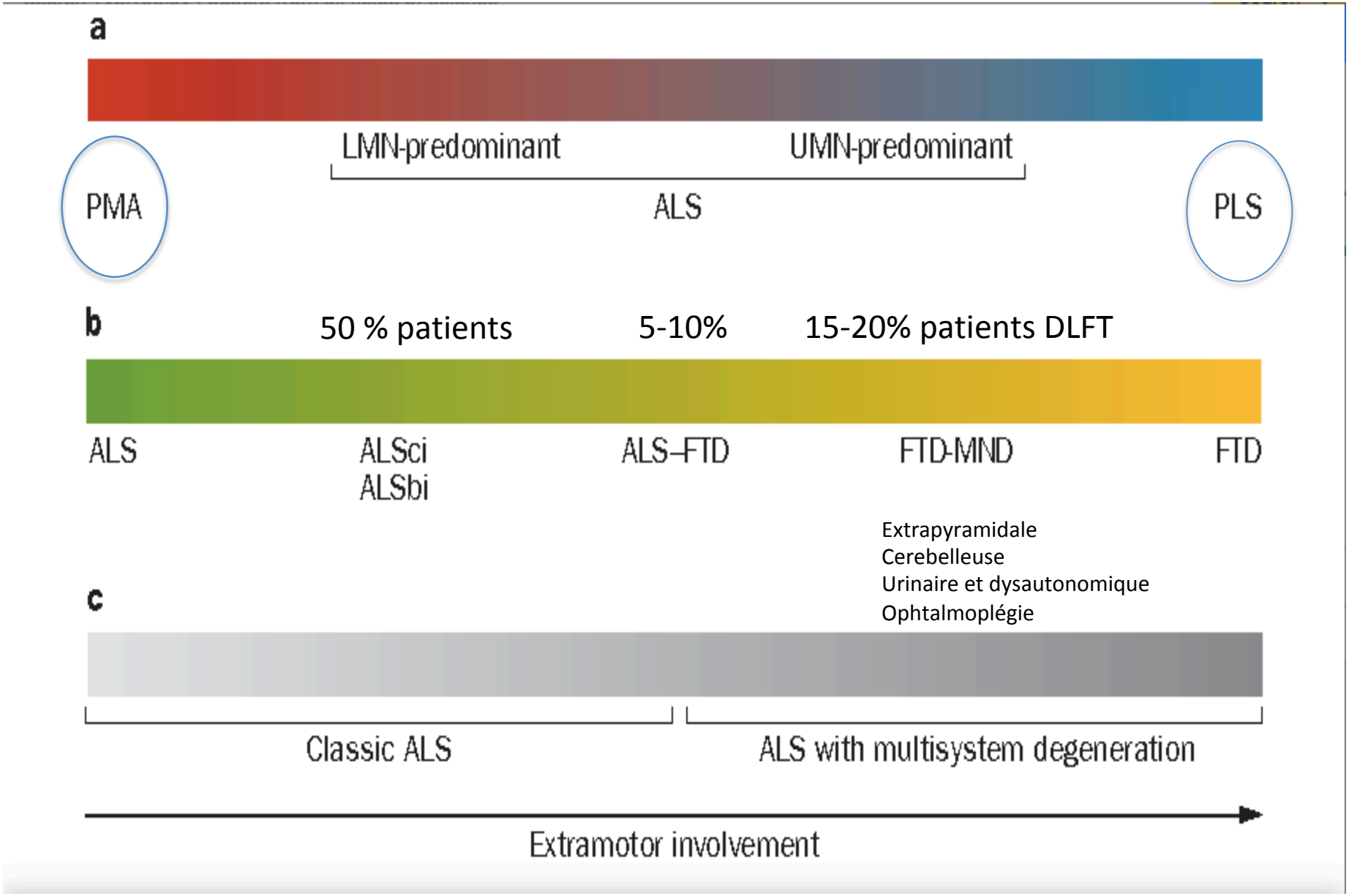


(Swinnen et al., 2014)





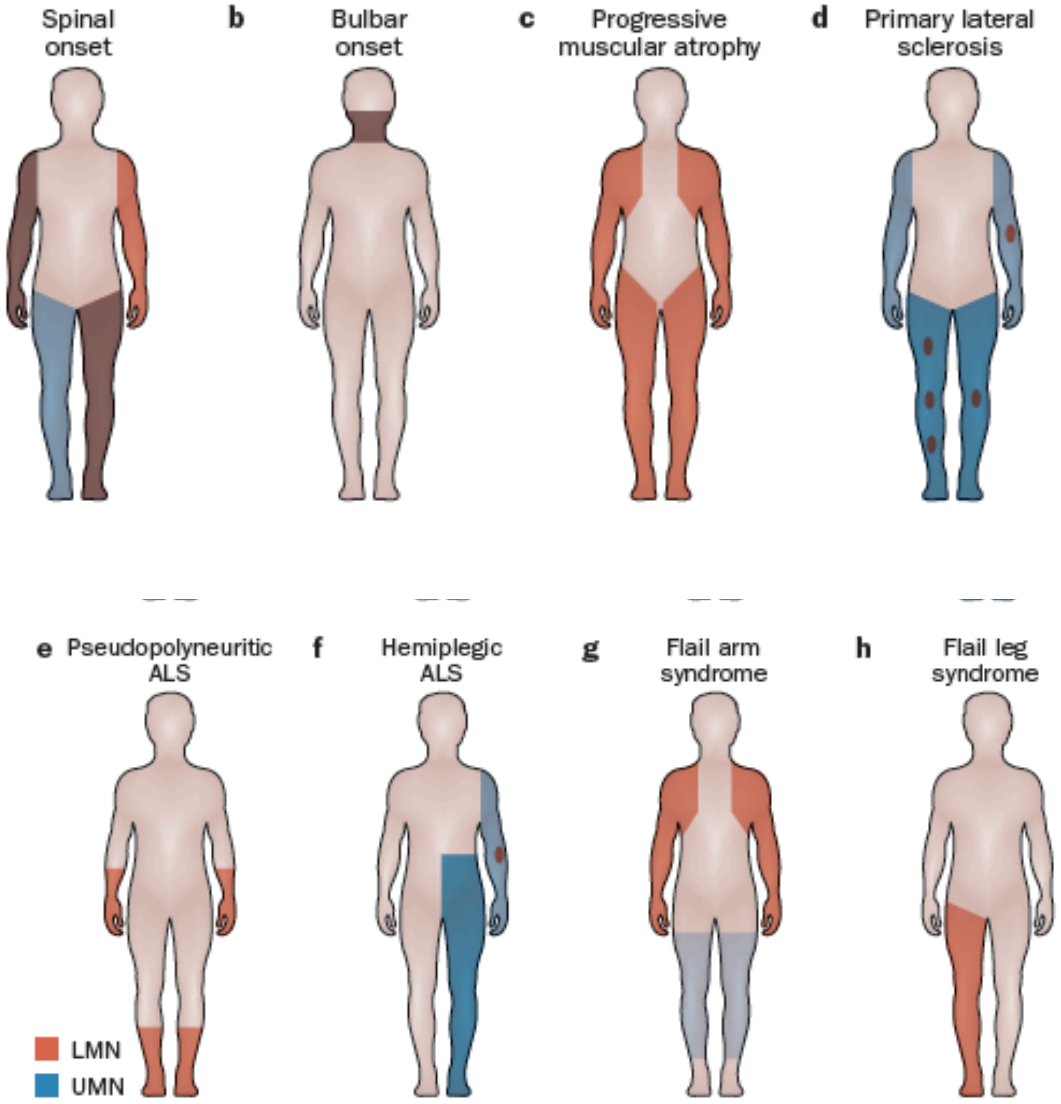
Un spectre hétérogène : moteur et extra-moteur

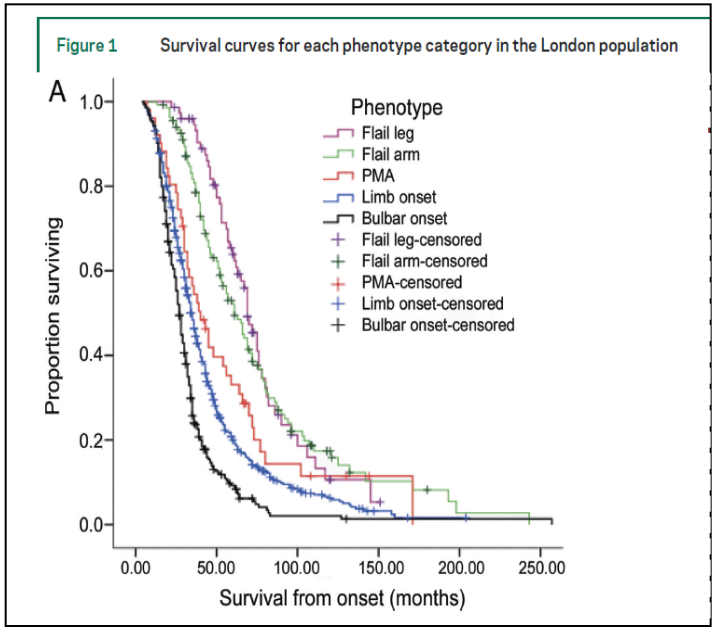


Facteurs modulant le phénotype

- Siège initial de l'atteinte motrice
- Type atteinte motrice MNp/NMC
- Age
- Sexe
- Degré atteinte extramotrice

Phénotypes de la SLA





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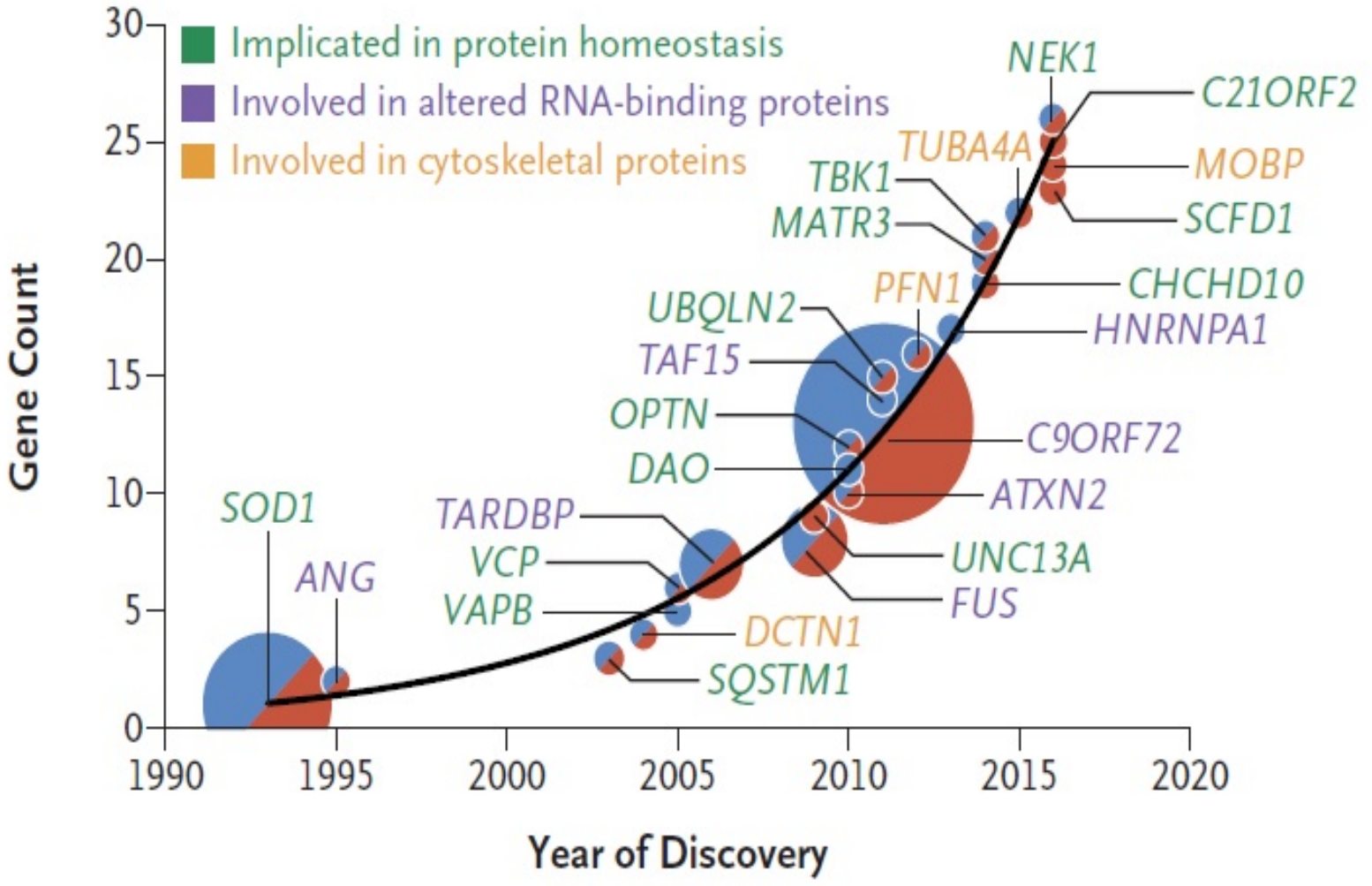
Une génétique complexe

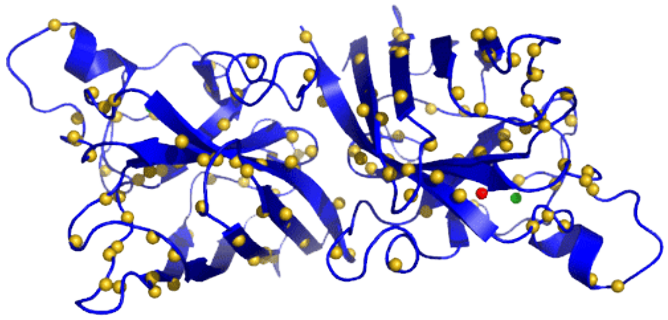


(Renton et al., 2014)

Gène SOD1

(Rosen et al, Nature 1993)

- Plus de 150 mutations à ce jour
  - Remplacement d'une base
  - Délétions, rares

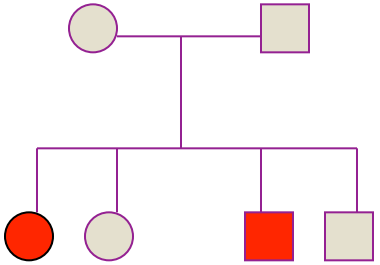


- Mutations Dominantes sauf:
  - D96N
  - D90A, la plus fréquente au monde et en France

- Identifiées dans 25 % des SLAF multigénérationnelles

Phénotype lié à la mutation D90A

- La plus fréquente des mutations SOD1
- Transmission Récessive autosomique
- Phénotype:
  - Début : 14 à 100 ans
  - Début aux MI, toujours
  - Evolution lente (>10 ans)
  - Cliniquement typique de SLA
- Origine suédoise



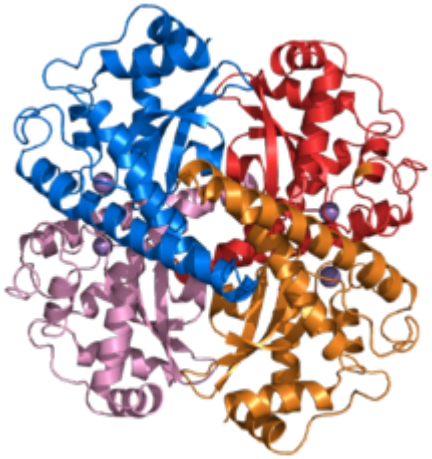
Phénotype lié à la mutation SOD1 A4V

- La plus fréquente au monde
- Age de début : 47+/- 13,7 ans
- Phénotype
  - Site de début: Membres inférieurs
  - Tableau d'atteinte pure du NMp
  - Pas d'atteinte du NMc
  - Jamais d'atteinte bulbaire
- Durée d'évolution très courte: 1,4 an


D90A
I113T
G41S
R115G
D90A
L144F
A4V
I112M

En faveur d'une mutation de SOD1

- Prédominance des débuts aux MI
- Rarement formes bulbaires
- Pas de troubles cognitifs
- Grande variabilité intra et interfamiliale
- Age de début: de 20 à 94 ans
- Pénétrance variable



En faveur d'une mutation TARDBP

Table 2 Characteristics of the 4 French ALS groups

	SALS group	FALS group	*SOD1* group	*TARDBP* group	*p* Value[a]
No.	737	192	58	28	
M/F	426/311	101/91	29/29	12/16	0.17, NS
Age at onset, y[b]	61.9 ± 12.1 (n = 737)	58.1 ± 11.6 (n = 172)	50.1 ± 12.0 (n = 56)	53.4 ± 12.7 (n = 28)	<0.0001
Bulbar, n (%)	291 (39.5)	61 (37.0)	6 (10.3)	6 (21.4)	<0.0001
Upper limb, n (%)	208 (28.2)	49 (29.7)	9 (15.5)	17 (60.7)	
Lower limb, n (%)	238 (32.3)	55 (33.3)	43 (74.1)	5 (17.9)	
Duration, mo[b]	30.7 (29.0–32.0) (n = 737)	28.6 (24.0–31.0) (n = 117)	41.0 (25.1–49.2) (n = 36)	63.0 (32.0–77.2) (n = 26)	0.009

Abbreviations: ALS = amyotrophic lateral sclerosis; FALS = familial amyotrophic lateral sclerosis; NS = not significant; SALS = sporadic amyotrophic lateral sclerosis.

[a] *p* Values for tests comparing the 4 groups together.

[b] For age at onset, values are mean ± SD; for duration, values are median (95% confidence interval); in parentheses, number of cases for which data are available.

TARDBP: Effet population

Table 3 Caucasian vs Asian *TARDBP*+ patients with ALS

	Caucasian	Asian	Whole group	*p* Value
No.	108	18	126	
M/F	63/45	8/10	71/55	NS
Age at onset, y[a]	53.6 ± 12.7 (n = 113)	55.1 ± 7.8 (n = 14)	53.5 ± 12.3 (n = 127)	NS
Bulbar onset, n (%)	18 (24.7)	11 (55.0)	29 (31.2)	
Upper limb onset, n (%)	39 (53.4)	5 (25.0)	44 (47.3)	0.02[b]
Lower limb onset, n (%)	16 (21.9)	4 (20.0)	20 (21.5)	
ALS duration, mo[a]	60 (48–72) (n = 92)	108 (15–144) (n = 12)	62 (48–77) (n = 104)	NS

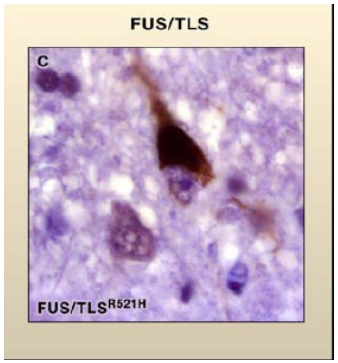
Abbreviations: ALS = amyotrophic lateral sclerosis; NS = not significant.

[a] For age, values are mean ± SD; for duration, values are median (95% confidence interval); in parentheses, number of cases for which data are available.

[b] Test between Caucasians and Asians for the 3 sites of onset.

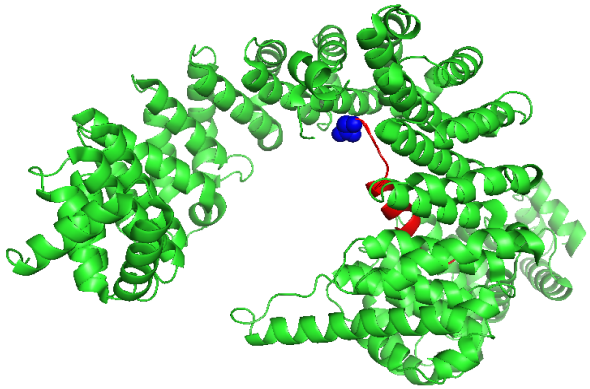
Formes classiques de SLA-mutation FUS

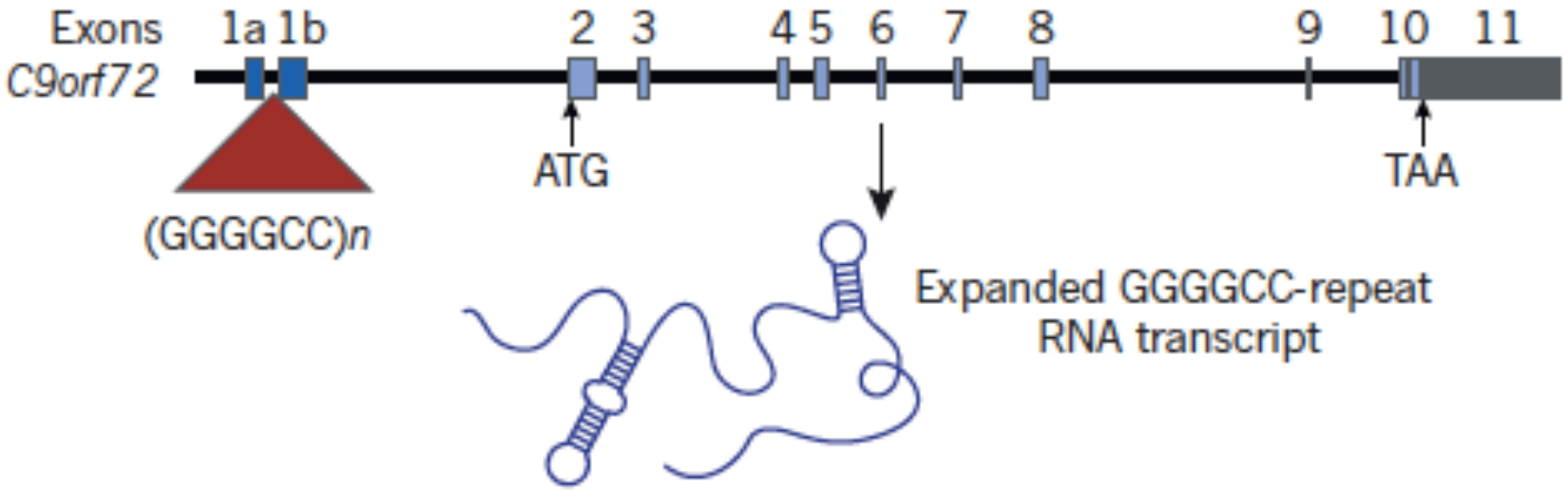
- Locus 16q12.
  - Mutation R521C, R521H++
  - Toutes dominantes sauf 1 (FALS du Cap Vert)
- *4% des SLA familiales (0.4% des SLA)*
- Forte pénétrance familiale
- ***Début précoce:***
  - SLA ayant début avant 40 ans, 35% de mutations
- *Début cervical*
- *Evolution rapide*
- Atteinte NMc au second plan
- Troubles cognitifs

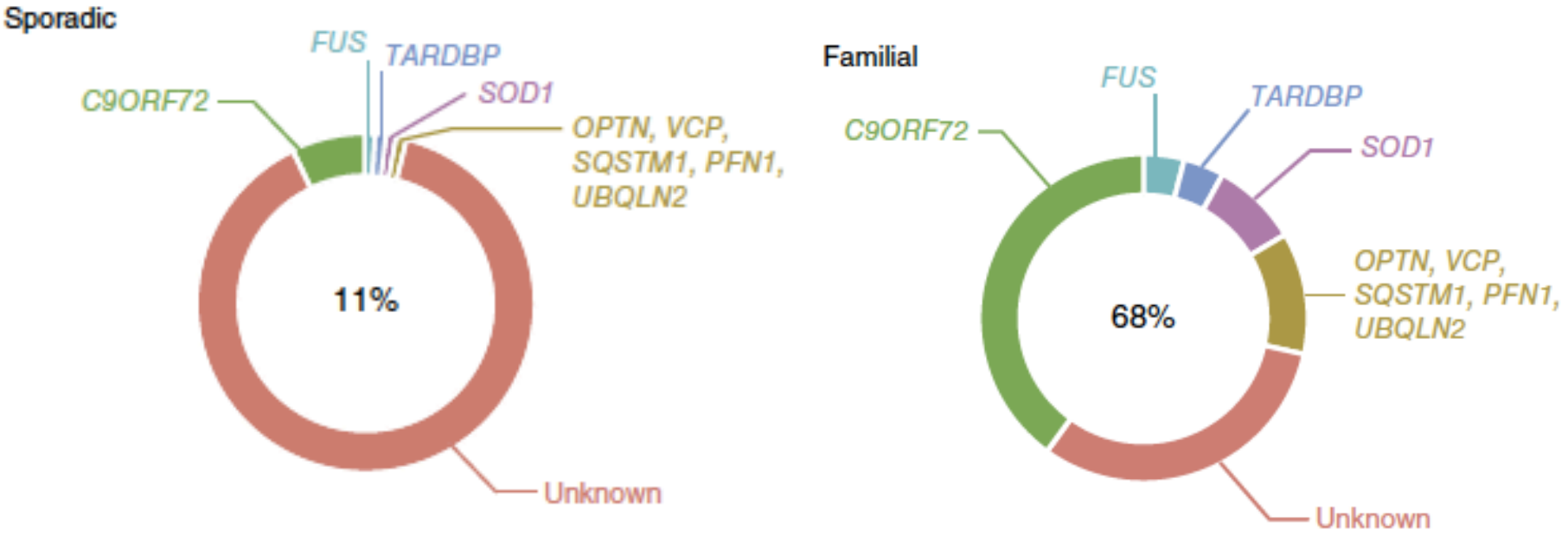


Formes juvéniles liées à une mutation FUS

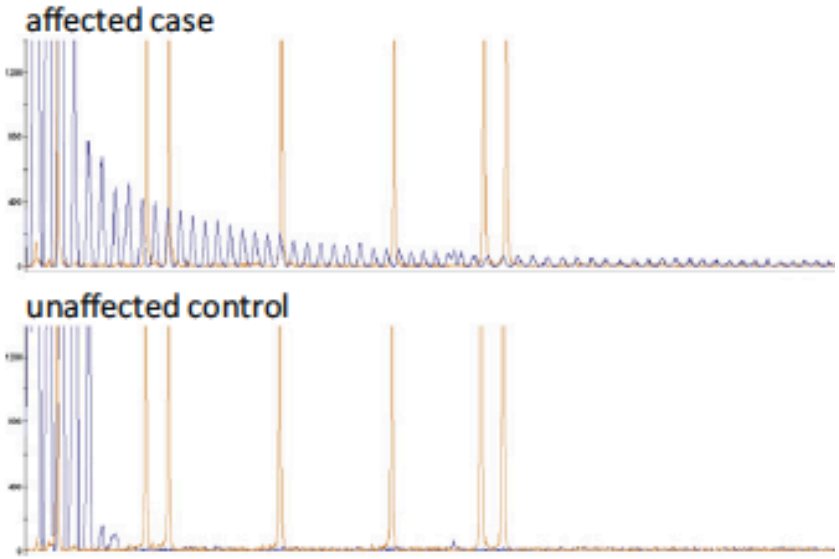
- Spécificités cliniques:
  - Essentiellement des formes sporadiques
  - Prédominance masculine
  - Evolution fulgurante:
    - Médiane de survie de 12 mois

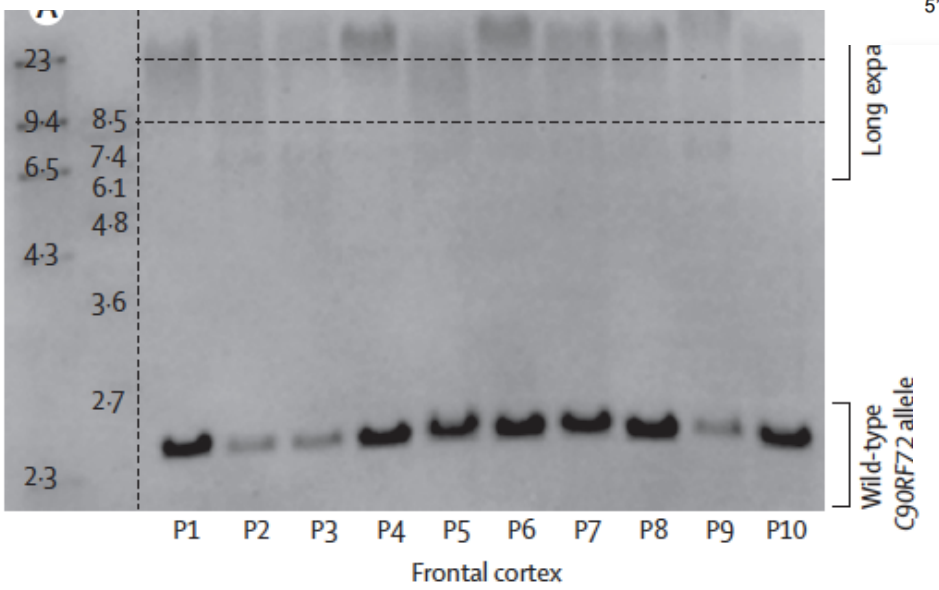


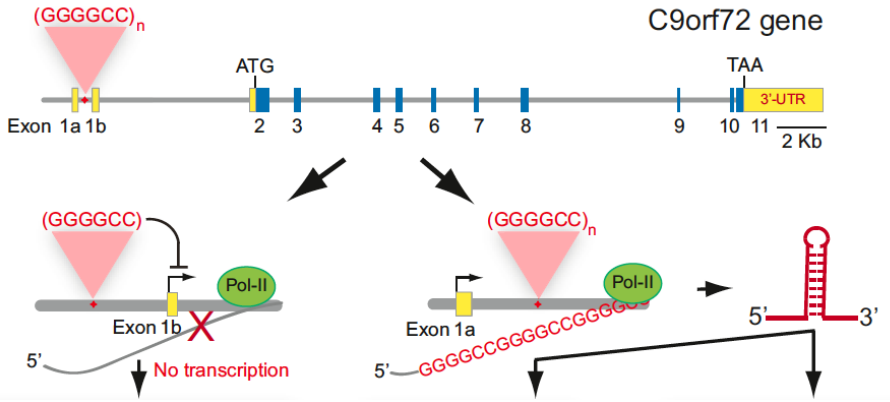

Exons
C9orf72
1a 1b
2 3
4 5 6 7 8
9 10 11
ATG
TAA
(GGGGCC)n
Expanded GGGGCC-repeat
RNA transcript

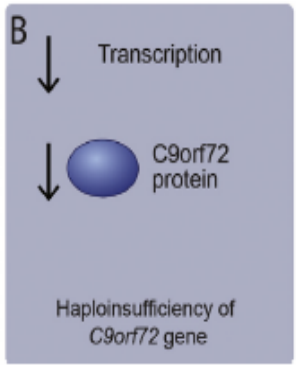

Sporadic
FUS
TARDBP
C9ORF72
SOD1
OPTN, VCP,
SQSTM1, PFN1,
UBQLN2
11%
Unknown
Familial
FUS
TARDBP
C9ORF72
SOD1
OPTN, VCP,
SQSTM1, PFN1,
UBQLN2
68%
Unknown

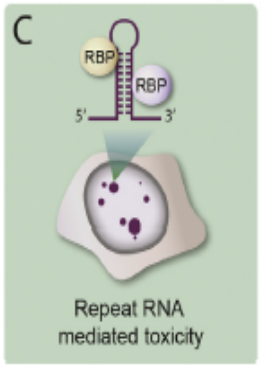
Seuil > 30 répétitions

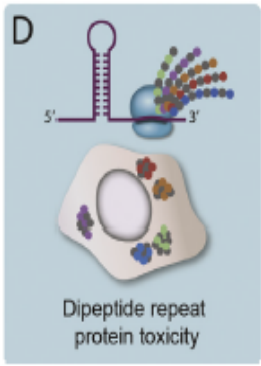












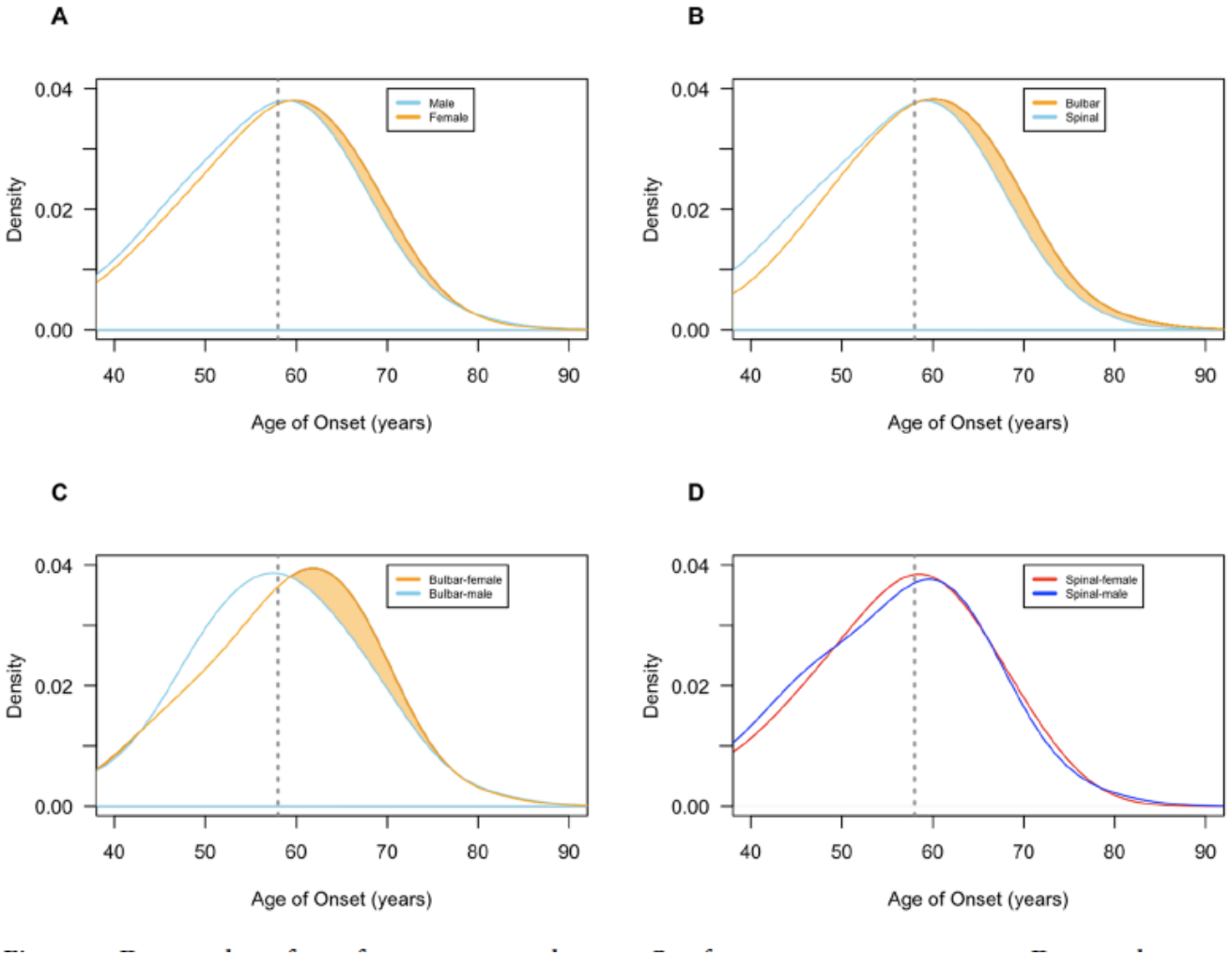
Phenotype difference between ALS patients with expanded repeats in *C9ORF72* and patients with mutations in other ALS-related genes

Table 1 Clinical comparison between groups of patients with a mutation in *SOD1, TARDBP, FUS*, hexanucleotide repeats in *C9ORF72* and patients with no identified genetic defect (other FALS)

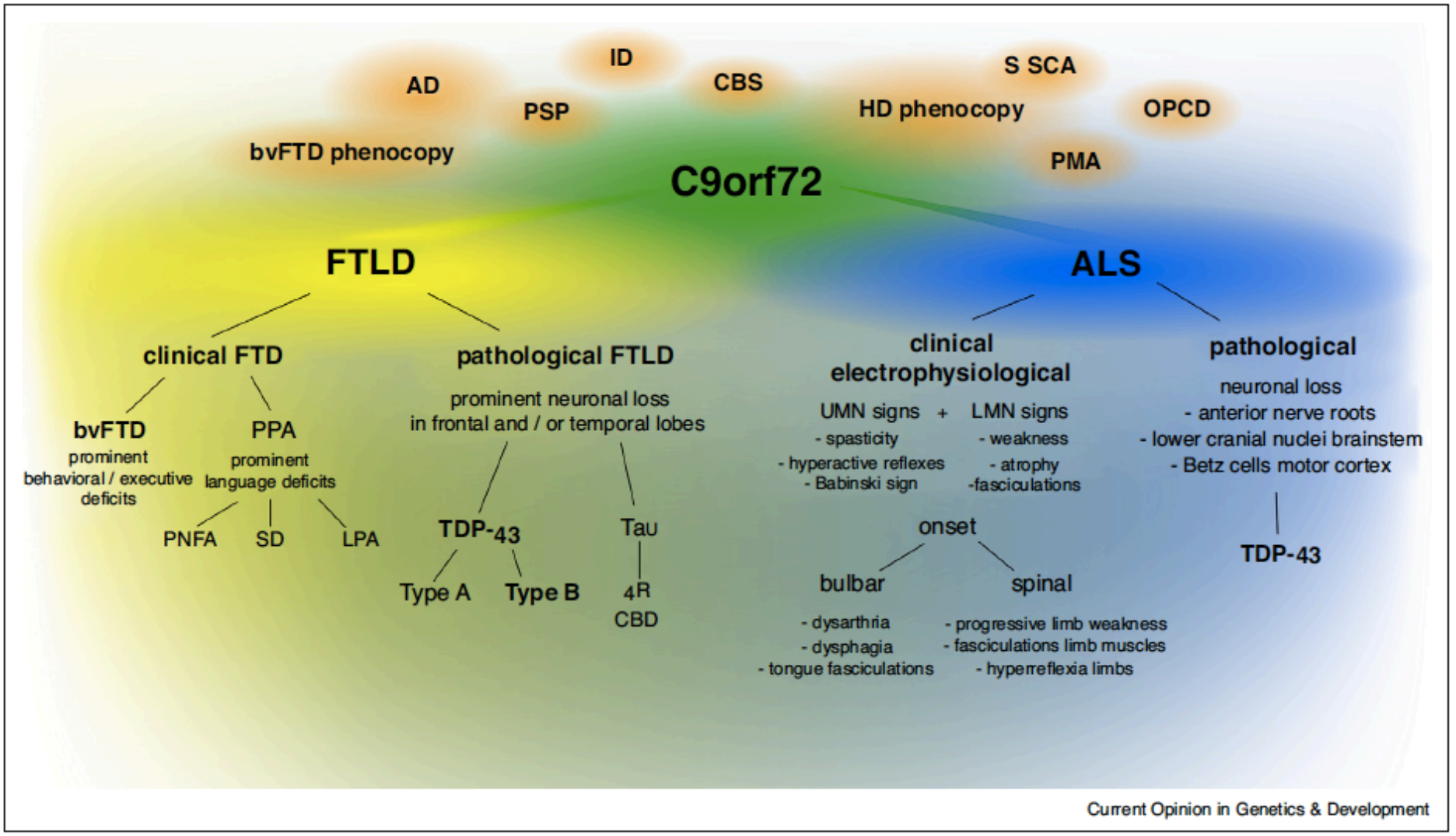
Patient groups	*C9ORF72*	*SOD1*	*TARDBP*	*FUS*	Other FALS
Age at onset (years)					
Mean (SE)	58 (1)	51 (2)	52 (3)	43 (2)	60 (2)
Median	57	51	57	40	61
Range	30–81 (n=120)	21–73 (n=46)	27–78 (n=18)	25–68 (n=36)	32–85 (n=70)
Disease duration (months)*					
Mean (SE)	33 (2)	81 (12)	56 (8)	34 (4)	66 (12)
Median	29	49	48	28	39
Range	3–85 (n=112)	4–252 (n=44)	20–156 (n=18)	9–88 (n=32)	8–336 (n=58)
Bulbar onset†					
Ratio of patients	48/120	3/41	2/18	5/35	14/69
FTD‡					
Ratio of patients	27/67	0/27	2/18	1/20	5/30
Gender					
M:F ratio	1.5:1 (n=130)	2.1:1 (n=81)	1.2:1 (n=56)	1:1.7 (n=27)	1.1:1 (n=40)

*Disease duration data included censored data (11 for C9ORF72, 8 for *SOD1*, 1 for *TARDBP*, 1 for *FUS* and 11 for other FALS).
†The fraction represents the number of patients with bulbar onset/the total number of patients for whom site of onset information was available.
‡The fraction represents the number of patients with frontotemporal dementia (FTD)/the total number of patients who were examined for cognitive deficits.
n, number of patients with the information available.

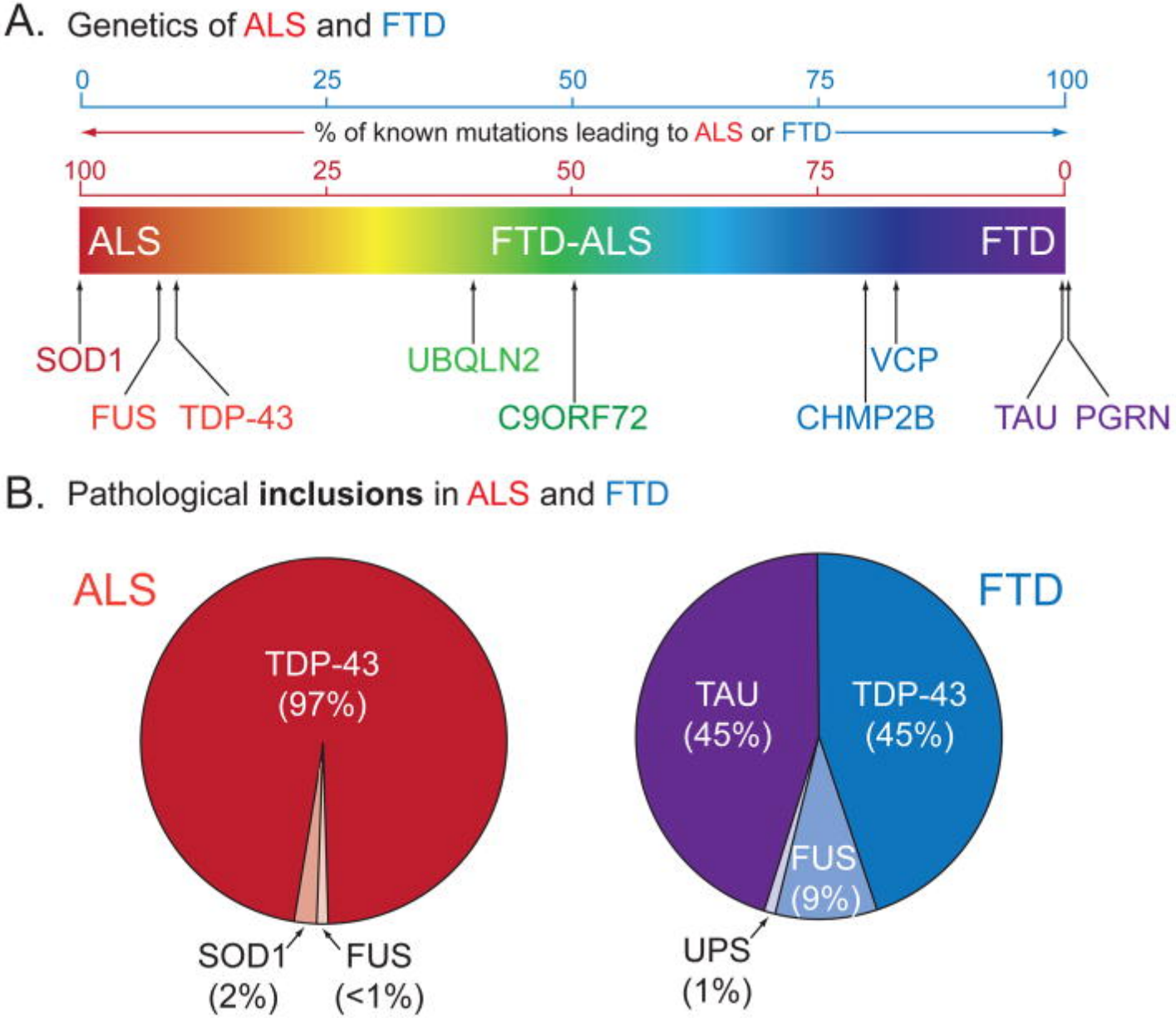
Age-related penetrance of the C9orf72 repeat expansion



Quel phénotype lié à C9ORF72?



Continuum SLA/DLFT



doi:10.1093/brain/awr366
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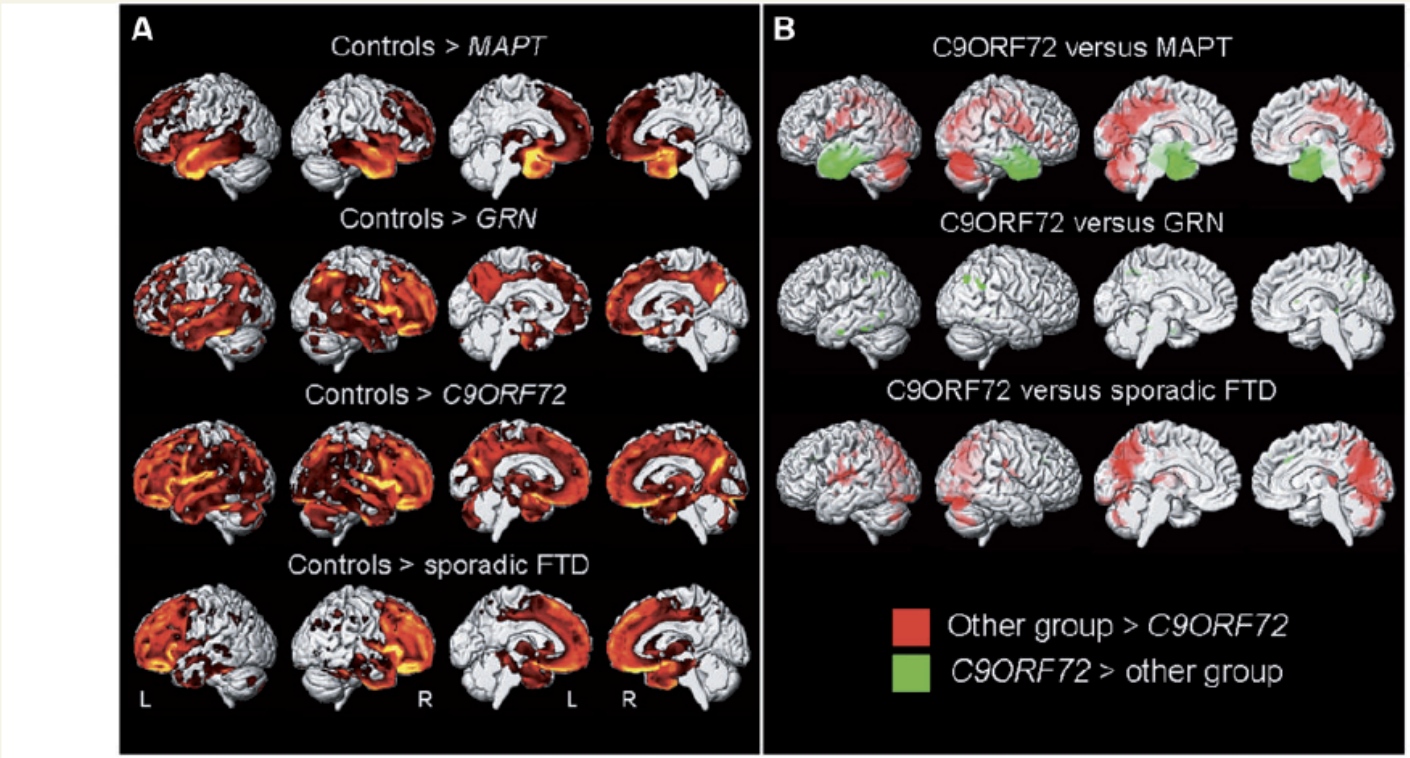


Figure 1 Results of the voxel-based morphometry analysis of grey matter volume. (**A**) Patterns of grey matter loss in *MAPT*, *GRN*, *C9ORF72* and sporadic FTD groups compared with controls, at $P < 0.05$ (corrected for multiple comparisons using family-wise error). (**B**) Differences in grey matter volume between the *C9ORF72* group and the other disease groups, at $P < 0.001$ (uncorrected for multiple comparisons). Results are shown in 3D renderings of the brain.

C9orf72 : Atrophie symétrique lobes frontaux dorsolatéral, médial et orbito-frontal

Tau : Atrophie temporale antéro médiale

Progranuline : Atrophie temporo pariétale

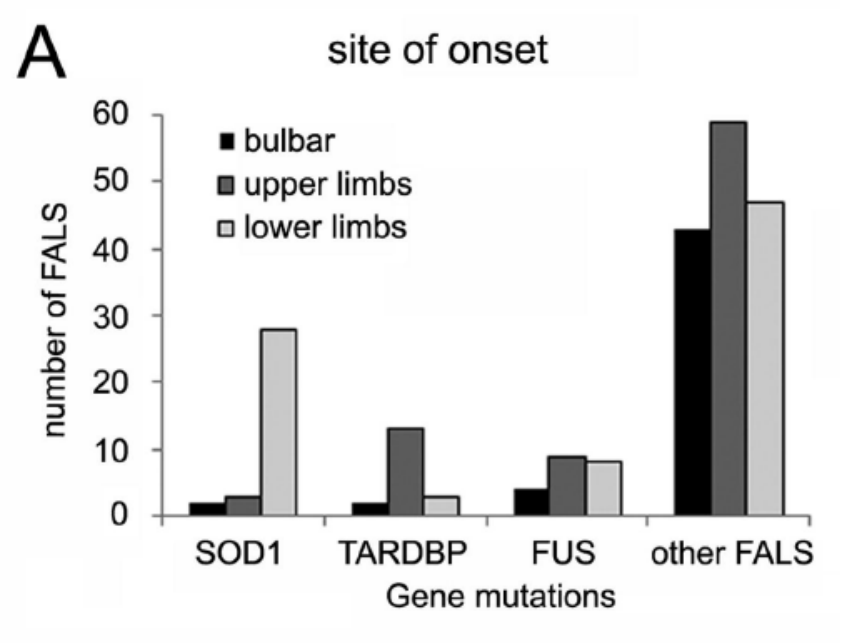
Psychiatric Presentations of *C9orf72* Mutation: What Are the Diagnostic Implications for Clinicians?

Simon Ducharme, M.D., M.Sc., F.R.C.P.(C), Sepideh Bajestan, M.D., Ph.D., Bradford C. Dickerson, M.D., Valerie Voon, M.D., Ph.D.

- Psychoses: 21-56%
  - Psychoses de révélation tardive
  - Habituellement 10% dans les DFT sporadiques
  - Illusions et Hallucinations multimodales
- Troubles bipolaires de révélation tardive
  - Troubles cognitifs
  - Catatonie
- Formes classiques de schizophrénie et bipolaires : 0,1%

Corrélations génotype-phénotype

- Expansion C9ORF72 :
  - mutation la plus fréquente après 40 ans
  - Début bulbaire
  - Association DFT-Troubles psychiatriques-Phénocopie HD
- Mutation Fus:
  - forme juvénile et formes les plus précoces/prédominance masculine
  - Evolution rapide
  - Analyse de trio : mutations de novo Fus des SLA sporadiques
- Mutations SOD1 :
  - Atteinte fréquente des membres inférieurs
  - Prédominance atteinte du MNp
  - Progression bi-modale
    - Formes rapides G41S
    - Formes très lentes N139D
  - Evolution hétérogène au sein d'une même famille avec même mutation
- Mutations TARDP :
  - Atteinte des membres supérieurs
  - Atteinte bulbaire associée
  - Atteinte frontale



Conclusion

- Génétique complexe
- 4 gènes majeurs
- Génotypage systématique SOD1 et C9orf72
  - Oligonucléotides antisens Tofersen
- Faire systématiquement arbre généalogique
- Rechercher antécédents SLA-DFT-Troubles psychiatriques
- Validation du caractère pathogène par RCP
- Diagnostic présympto : C9orf72++ et SOD1