# ALS: A SYSTEMIC DISEASE?

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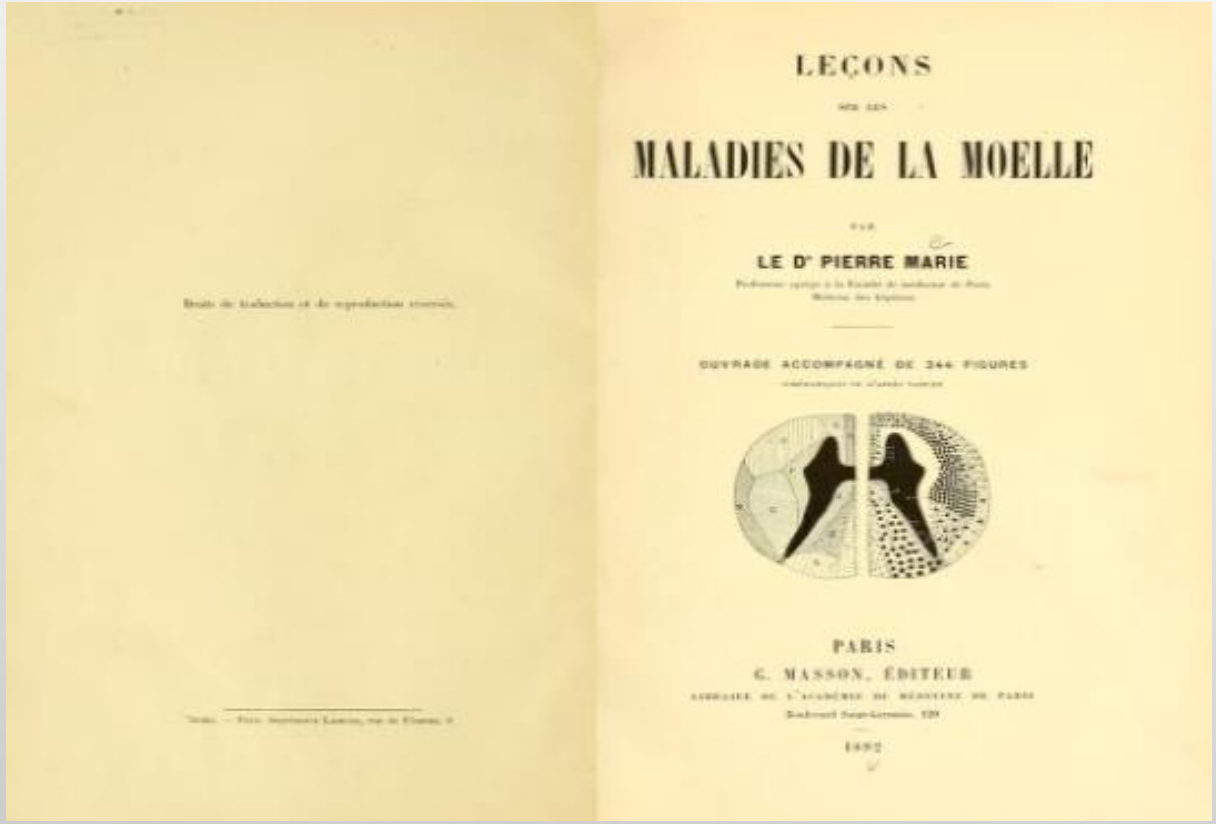
# BACKGROUND


LEÇONS

MALADIES DE LA MOELLE

LE Dr PIERRE MARIE

OUVRAGE ACCOMPAGNÉ DE 344 FIGURES

PARIS

G. MASSON, ÉDITEUR

1892

Marie P. Lecons sur les maladies de la moelle [1892]

Early studies of ALS, beginning in the 1880s, recognized that dementia often accompanied ALS, but this association has been largely neglect until recent years.

# BACKGROUND (2)

*Journal of Neurology, Neurosurgery, and Psychiatry* 1984;**47**:953–959

## Presenile dementia with motor neuron disease in Japan: clinico-pathological review of 26 cases

YOSHIO MITSUYAMA

*From the Department of Psychiatry, Miyazaki Medical College, Miyazaki, Japan*

SUMMARY The clinico-pathological findings of 26 cases of presenile dementia with motor neuron disease in Japan are reviewed. The characteristic features include: (1) Progressive dementia with slowly progressive onset in the presenile period. (2) Neurogenic muscular wasting during the course of illness. (3) A duration of illness to death of from one to three years. (4) Absence of extrapyramidal symptoms and definite sensory deficits. (5) No characteristic abnormalities in the CSF or EEG. (6) No known parental consanguinity of familial occurrence. (7) Non-specific mild degenerative changes throughout the CNS without evidence of cerebrovascular disease or primary degenerative dementia, but with the presence of pathological findings of motor neuron disease. The possibility that this is a new disease entity is suggested.

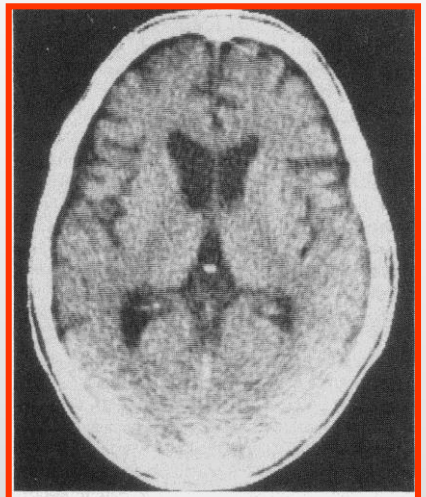


Fig 6 *Case 3; CT scan shows moderate cerebral atrophy.*

*Brain* (1981), **104**, 217–247

## AMYOTROPHIC LATERAL SCLEROSIS AND ITS ASSOCIATION WITH DEMENTIA, PARKINSONISM AND OTHER NEUROLOGICAL DISORDERS: A REVIEW

*by* ARTHUR J. HUDSON

*(From the Department of Clinical Neurological Sciences, University of Western Ontario and the University Hospital, 339 Windermere Road, London, Ontario N6A 5A5, Canada)*

The idea of ALS as a multisystem disorder remained relatively unexplored since the beginning of 1980s.

Gradually, in the following years, a more specific association between motor neuron disease and frontotemporal dementia was recognised.

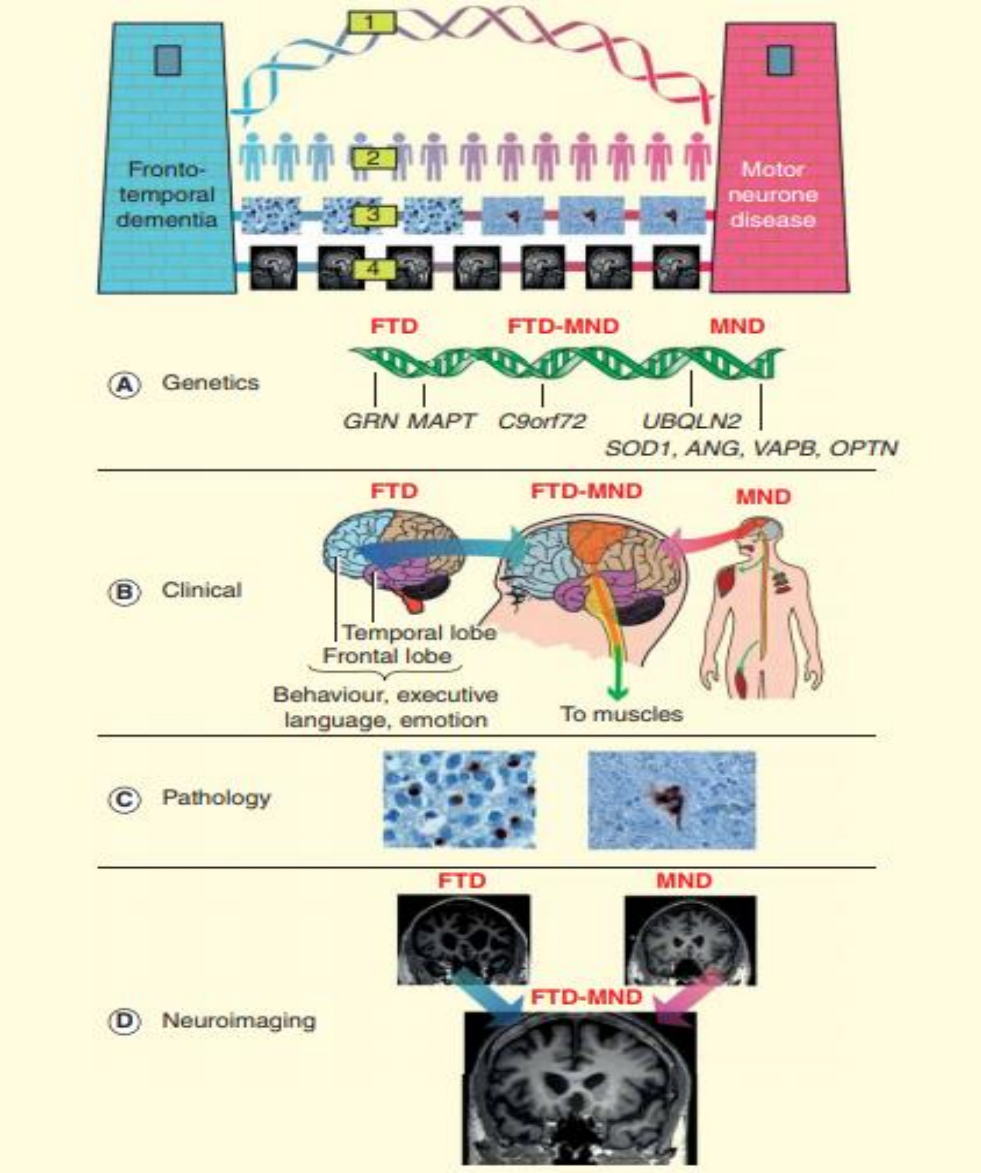
## The frontotemporal dementia-motor neuron disease continuum

James R Burrell, Glenda M Halliday, Jillian J Kril, Lars M Ittner, Jürgen Götz, Matthew C Kiernan, John R Hodges

Early reports of cognitive and behavioural deficits in motor neuron disease might have been overlooked initially, but the concept of a frontotemporal dementia-motor neuron disease continuum has emerged during the past decade. Frontotemporal dementia-motor neuron disease is now recognised as an important dementia syndrome, which presents substantial challenges for diagnosis and management. Frontotemporal dementia, motor neuron disease, and frontotemporal dementia-motor neuron disease are characterised by overlapping patterns of TAR DNA binding protein (TDP-43) pathology, while the chromosome 9 open reading frame 72 (*C9orf72*) repeat expansion is common across the disease spectrum. Indeed, the *C9orf72* repeat expansion provides important clues to disease pathogenesis and suggests potential therapeutic targets. Variable diagnostic criteria identify motor, cognitive, and behavioural deficits, but further refinement is needed to define the clinical syndromes encountered in frontotemporal dementia-motor neuron disease.

Lancet 2016

# ALS AND FTD: A DISEASE CONTINUUM




Overlap between motor neuron disease and frontotemporal dementia occurs at clinical, genetic, pathological and neuroimaging levels.

**A pictorial illustration of the ALS-FTD continuum showing the multiple levels of overlap between the conditions.**
Motor neuron disease-frontotemporal dementia: a clinical continuum. Devenney e. et al. [2015]

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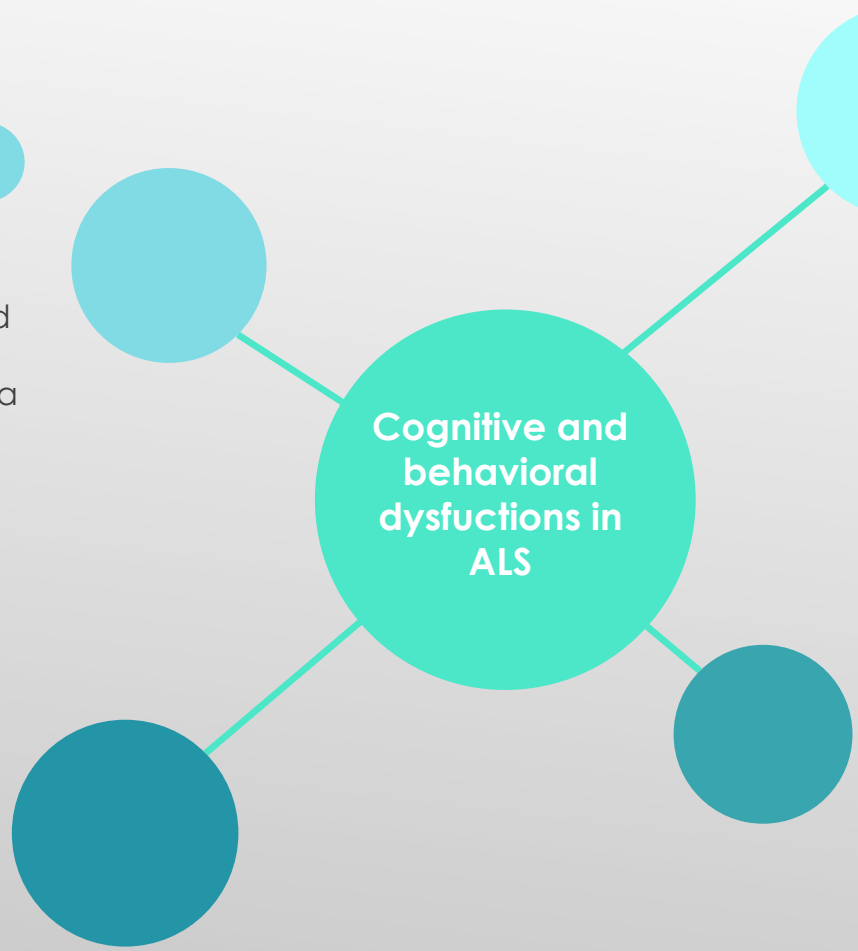
# FRONTOTEMPORAL DYSFUCTION IN MND




## Executive function

Executive abilities help with decision making, motivation and inhibitory control.
Verbal fluency has emerged as a robust marker of executive dysfuction

## Language

Language impairments in motor neuron disease are similar to those seen in the language phenotypes of frontotemporal dementia

## Social cognition

Social cognition, theory of mind and emotional processing are essential for effective human interactions

## Behavior

Behavioural changes in ALS overlap with those noted in FTD

# EXECUTIVE FUNCTION IN ALS

## Amyotrophic lateral sclerosis patients show executive impairments on standard neuropsychological measures and an ecologically valid motor-free test of executive functions

**Vita Štukovnik,[1] Janez Zidar,[1] Simon Podnar,[1] and Grega Repovš[2]**

[1]Institute of Clinical Neurophysiology, Division of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[2]Department of Psychology, University of Ljubljana, Ljubljana, Slovenia

The study aimed to evaluate the nature and extent of executive deficits in nondemented amyotrophic lateral sclerosis (ALS) patients. A total of 22 ALS patients and 21 matched controls were compared on standard neuropsychological tests of executive functions with appropriate control for motor impairment and on an ecologically valid motor-free test of executive functions, the Medication Scheduling Task (MST). Our results show that motor dysfunction can present a significant confound when using standard neuropsychological measures; however, even when accounting for motor disabilities, ALS patients show a robust pattern of cognitive dysfunctions. Additionally, MST was shown to be a sensitive measure of cognitive impairment, providing an important insight into cognitive processes relevant for patients' daily living.

***Keywords:*** Amyotrophic lateral sclerosis; Executive dysfunction; Motor-free assessment of executive functions; Ecological validity; Medication Scheduling Task.

J Clin Exp Neuropsychol 2010

**Verbal fluency tests**, often adapted to control for dysarthria, are robust measures of executive dysfunction in motor neuron disease and frontotemporal dementia-motor neuron disease.

# LANGUAGE DEFICITS IN ALS

## Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease–dementia–aphasia syndrome

Thomas H. Bak,[1,2] Dominic G. O'Donovan,[3] John H. Xuereb,[3] Simon Boniface[4] and John R. Hodges[1,2]

[1]*Medical Research Council Cognition and Brain Sciences Unit,* [2]*The University of Cambridge Neurology Unit and* [4]*The Department of Clinical Neurophysiology, Addenbrooke's Hospital, Cambridge and* [3]*The University of Cambridge Department of Pathology, Cambridge, UK*

*Correspondence to: Professor John R. Hodges, MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK*
*E-mail: john.hodges@mrc-cbu.cam.ac.uk*

**Summary**

**We report six patients with clinically diagnosed and electrophysiologically confirmed motor neurone disease (MND), in whom communication problems were an early and dominant feature. All patients developed a progressive non-fluent aphasia culminating in some cases in complete mutism. In five cases, formal testing revealed deficits in syntactic comprehension. Comprehension and production of verbs were consistently more affected those that of nouns and this effect remained stable upon subsequent testing, despite overall deterioration. The classical signs of MND, including wasting, fasciculations and severe bulbar symptoms, occurred over the following 6–12 months. The behavioural symptoms ranged from mild anosognosia to personality change implicating frontal-lobe dementia. In three cases, post-mortem examination has confirmed the clinical diagnosis of MND–dementia. In addition to the typical involvement of motor and premotor cortex, particularly pronounced pathological changes were observed in the Brodmann areas 44 (Broca's area) and 45. The finding of a selective impairment of verb/action processing in association with the dementia/aphasia syndrome of MND suggests that the neural substrate underlying verb representation is strongly connected to anterior cortical motor systems.**

Brain 2001

**Naming** and **semantic comprehension** deficits are frequently present and **phonological and syntactic deficits** can also exist.

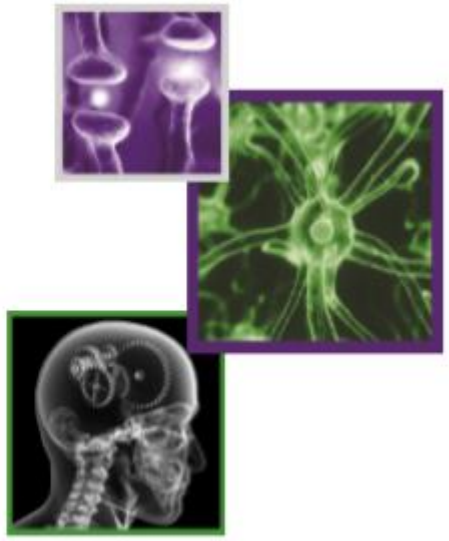
**Verb processing** has been reported to be selectively impaired in MND, while noun-processing deficits are more prevalent in cases of bvFTD.

# SOCIAL COGNITION AND EMOTIONAL PROCESSING

REVIEW

*For reprint orders, please contact: reprints@futuremedicine.com*

## Social cognition in amyotrophic lateral sclerosis



Sharon Abrahams[1]

**SUMMARY** There is an overlap between amyotrophic lateral sclerosis and frontotemporal dementia. Approximately 15% of amyotrophic lateral sclerosis patients suffer from frontotemporal dementia characterized by behavioral change while a further third experience subtle executive dysfunction (typically letter fluency deficits) and corresponding prefrontal changes. Behavior change appears prevalent with apathy being the most prominent feature. Reports of social and emotional cognition deficits are increasing. Deficits have been described on theory of mind tasks including interpretation of stories and cartoons, faux pas detection and in the judgment of preference based on direction of eye-gaze. Impairments in emotional face and prosody perception and emotional enhancement of memory have been reported, and decision making (with and without risk) appears affected. The role of executive dysfunction in this social cognition deficit remains unresolved and more direct evidence of oribitofrontal involvement has yet to be found. Implications for healthcare provision are discussed with deterioration of social interaction with carers predicted.

Patients with either motor neuron disease or frontotemporal dementia-motor neuron disease have **impareid social cognition, theory of mind,** and **emotional processing.**

Neurodegener Dis Manag 2011

# PATHOLOGY

2006

The discovery of a trans-activating responsive (Tar) sequence DNA-binding protein (TDP-43) contributed pathological evidence to support the notion of an overlap between MND and FTD.

**TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis**

Tetsuaki Arai [a,1,*], Masato Hasegawa [b,1,*], Haruhiko Akiyama [a], Kenji Ikeda [c], Takashi Nonaka [b], Hiroshi Mori [d], David Mann [e], Kuniaki Tsuchiya [f], Mari Yoshida [g], Yoshio Hashizume [g], Tatsuro Oda [h]

[a] *Department of Psychogeriatrics, Tokyo Institute of Psychiatry 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo 156-8585, Japan*
[b] *Department of Molecular Neurobiology, Tokyo Institute of Psychiatry 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo 156-8585, Japan*
[c] *Zikei hospital 100-2 Urayasuhonmachi, Okayama-shi, Okayama 702-8508, Japan*
[d] *Department of Neuroscience, Osaka City University School of Medicine, 1-4-3 Asahimachi, Abenoku, Osaka 545-8585, Japan*
[e] *Greater Manchester Neurosciences Centre, University of Manchester, Hope Hospital, Salford M6 8HD, UK*
[f] *Department of Laboratory Medicine and Pathology, Tokyo Metropolitan Matsuzawa Hospital, 2-1-1 Kamikitazawa, Setagaya-ku, Tokyo 156-0057, Japan*
[g] *Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University, 21 Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan*
[h] *Department of Neuropsychiatry, National Shimofusa Mental Hospital, Chiba 266-0007, Japan*

Received 2 October 2006
Available online 30 October 2006

**Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis**

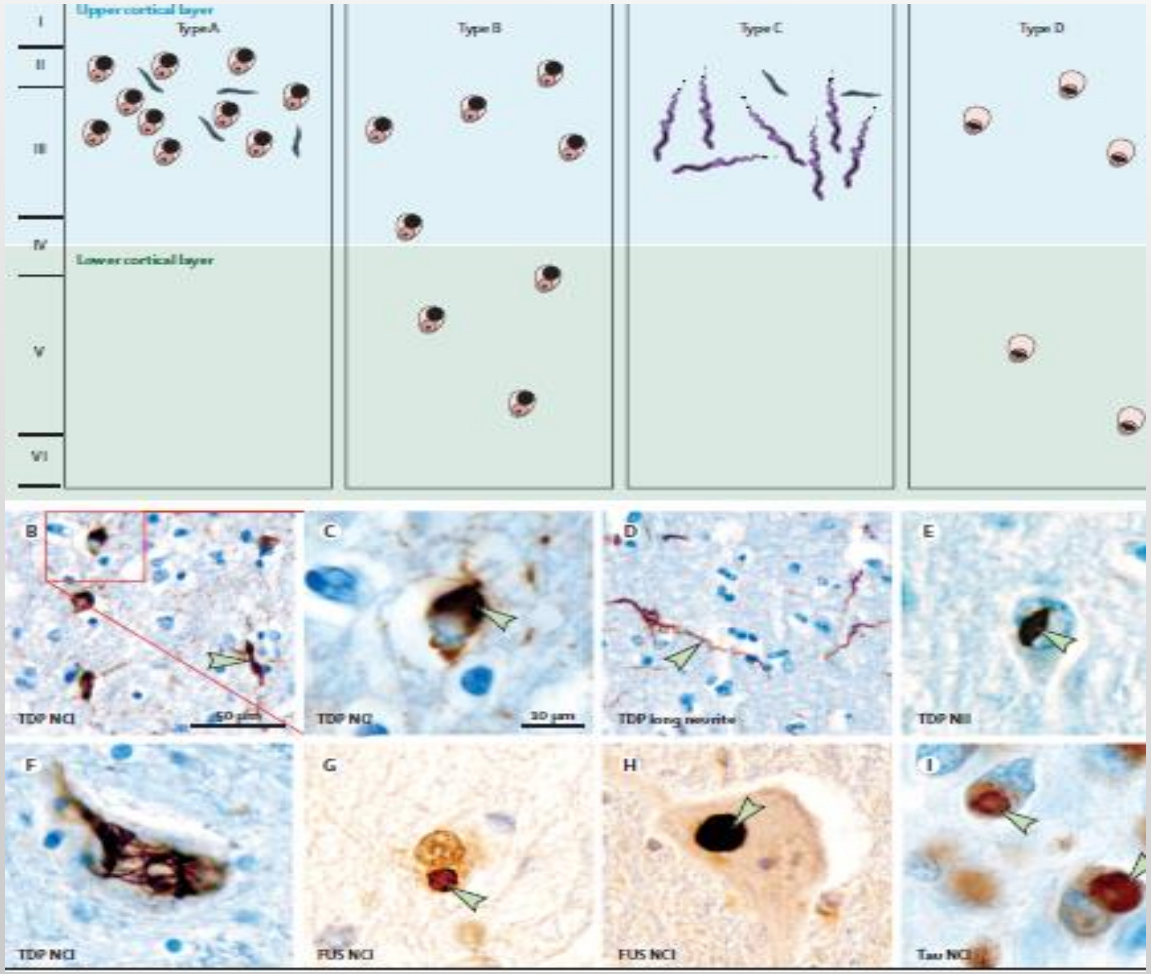
Manuela Neumann,[1,11]* Deepak M. Sampathu,[1]* Linda K. Kwong,[1]* Adam C. Truax,[1] Matthew C. Micsenyi,[1] Thomas T. Chou,[2] Jennifer Bruce,[1] Theresa Schuck,[1] Murray Grossman,[3,4] Christopher M. Clark,[3,4] Leo F. McCluskey,[3] Bruce L. Miller,[6] Eliezer Masliah,[7] Ian R. Mackenzie,[8] Howard Feldman,[9] Wolfgang Feiden,[10] Hans A. Kretzschmar,[11] John Q. Trojanowski,[1,4,5] Virginia M.-Y. Lee[1,4,5]†

Ubiquitin-positive, tau- and α-synuclein–negative inclusions are hallmarks of frontotemporal lobar degeneration with ubiquitin-positive inclusions and amyotrophic lateral sclerosis. Although the identity of the ubiquitinated protein specific to either disorder was unknown, we showed that TDP-43 is the major disease protein in both disorders. Pathologic TDP-43 was hyperphosphorylated, ubiquitinated, and cleaved to generate C-terminal fragments and was recovered only from affected central nervous system regions, including hippocampus, neocortex, and spinal cord. TDP-43 represents the common pathologic substrate linking these neurodegenerative disorders.

Science, 2006

TDP-43 protein deposition has been reported in a subgroup of FTD patients without tau pathology, as well as the majority of familial and sporadic ALS cases.

# PATHOLOGY (2)



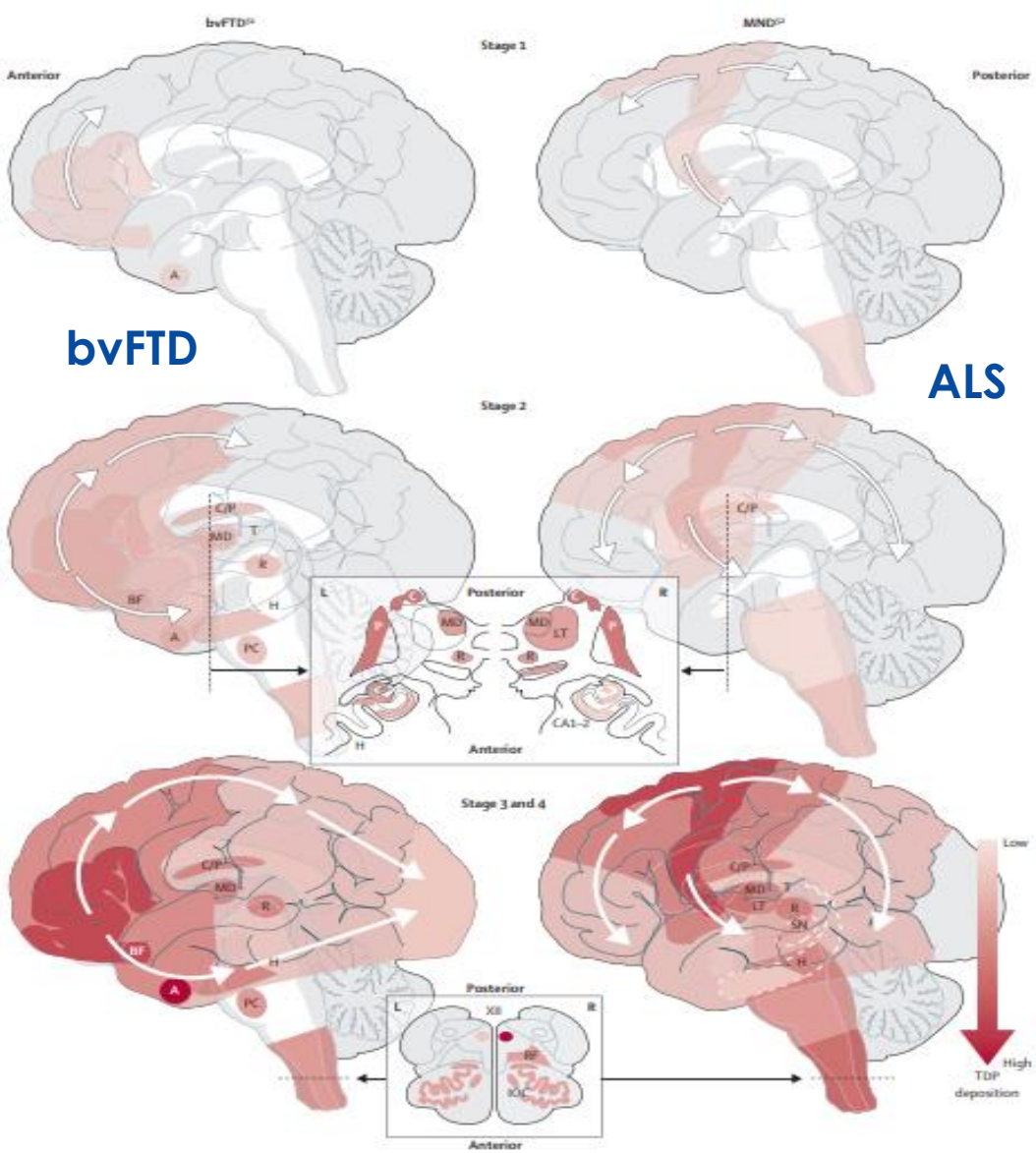

The frontotemporal dementia-motor neuron disease continuum. J.R. Burrell et al. [2016]

**Pathological inclusions found in frontotemporal dementia and motor neuron disease.**

In FTD, TDP-43 pathology varies in morphology and distribution with four different identified subtypes (type A-D).

In motor neuron disease, TDP-immunoreactive neuronal cytoplasmatic inclusions can be either skein-like (F) or Lewy body-like.

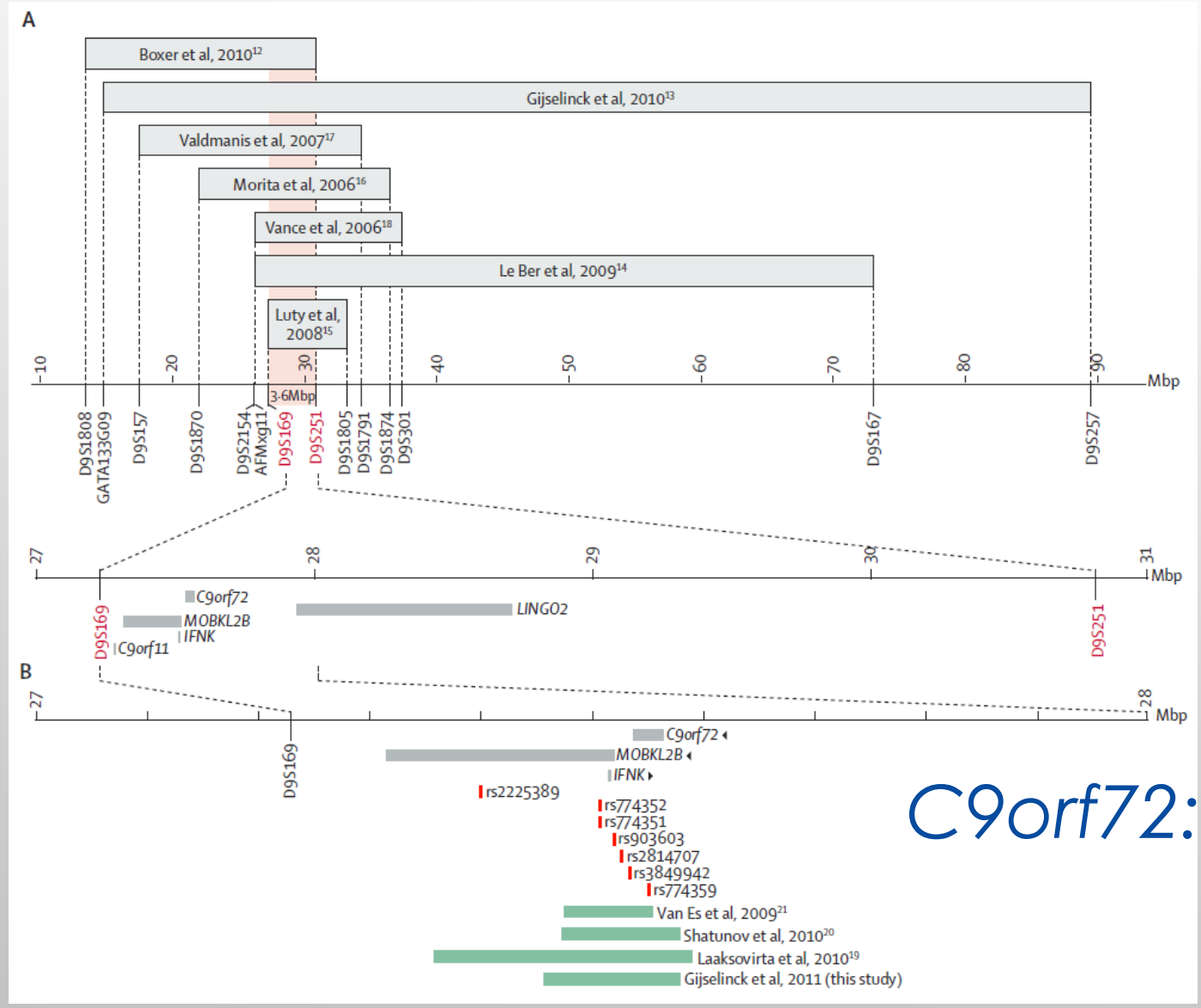
# PATHOLOGY (3)




Stages of TDP-43 deposition in behavioural variant-frontotemporal dementia compared with motor neuron disease.

The frontotemporal dementia-motor neuron disease continuum
J.R. Burrell et al. Lancet [2016]

# GENETIC: a futher piece of the overlap puzzle




**Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS**


Mariely DeJesus-Hernandez,[1,10] Ian R. Mackenzie,[2,10,*] Bradley F. Boeve,[3] Adam L. Boxer,[4] Matt Baker,[1] Nicola J. Rutherford,[1] Alexandra M. Nicholson,[1] NiCole A. Finch,[1] Heather Flynn,[5] Jennifer Adamson,[1] Naomi Kouri,[1] Aleksandra Wojtas,[1] Pheth Sengdy,[6] Ging-Yuek R. Hsiung,[6] Anna Karydas,[4] William W. Seeley,[4] Keith A. Josephs,[3] Giovanni Coppola,[7] Daniel H. Geschwind,[7] Zbigniew K. Wszolek,[8] Howard Feldman,[6,9] David S. Knopman,[3] Ronald C. Petersen,[3] Bruce L. Miller,[4] Dennis W. Dickson,[1] Kevin B. Boylan,[8] Neill R. Graff-Radford,[8] and Rosa Rademakers[1,*]


**A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD**

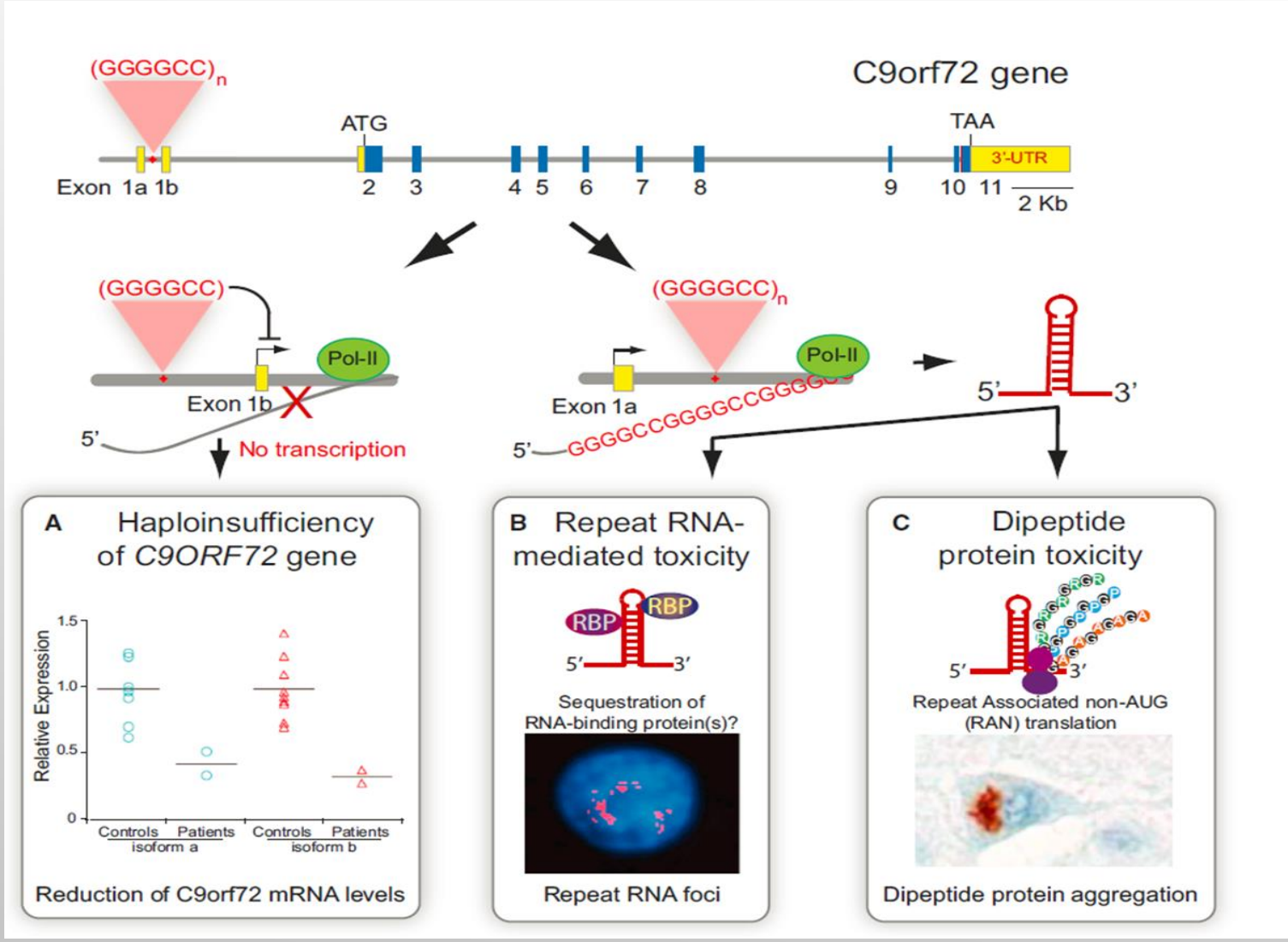

Alan E. Renton,[1,28] Elisa Majounie,[2,28] Adrian Waite,[3,28] Javier Simón-Sánchez,[4,5,28] Sara Rollinson,[6,28] J. Raphael Gibbs,[7,8,28] Jennifer C. Schymick,[1,28] Hannu Laaksovirta,[9,28] John C. van Swieten,[4,5,28] Liisa Myllykangas,[10] Hannu Kalimo,[10] Anders Paetau,[10] Yevgeniya Abramzon,[1] Anne M. Remes,[11] Alice Kaganovich,[12] Sonja W. Scholz,[2,13,14] Jamie Duckworth,[7] Jinhui Ding,[7] Daniel W. Harmer,[15] Dena G. Hernandez,[2,8] Janel O. Johnson,[1,8] Kin Mok,[8] Mina Ryten,[6] Danyah Trabzuni,[6] Rita J. Guerreiro,[6] Richard W. Orrell,[16] James Neal,[17] Alex Murray,[18] Justin Pearson,[3] Iris E. Jansen,[4] David Sondervan,[4] Harro Seelaar,[5] Derek Blake,[3] Kate Young,[6] Nicola Halliwell,[6] Janis Bennion Callister,[6] Greg Toulson,[6] Anna Richardson,[19] Alex Gerhard,[19] Julie Snowden,[19] David Mann,[19] David Neary,[19] Michael A. Nalls,[2] Terhi Peuralinna,[9] Lilja Jansson,[9] Veli-Matti Isoviita,[9] Anna-Lotta Kaivorinne,[11] Maarit Hölttä-Vuori,[20] Elina Ikonen,[20] Raimo Sulkava,[21] Michael Benatar,[22] Joanne Wuu,[23] Adriano Chiò,[24] Gabriella Restagno,[25] Giuseppe Borghero,[26] Mario Sabatelli,[27] The ITALSGEN Consortium,[28] David Heckerman,[29] Ekaterina Rogaeva,[30] Lorne Zinman,[31] Jeffrey D. Rothstein,[14] Michael Sendtner,[32] Carsten Drepper,[32] Evan E. Eichler,[33] Can Alkan,[33] Ziedulla Abdullaev,[34] Svetlana D. Pack,[34] Amalia Dutra,[35] Evgenia Pak,[35] John Hardy,[6] Andrew Singleton,[2] Nigel M. Williams,[3,28] Peter Heutink,[4,28] Stuart Pickering-Brown,[6,28] Huw R. Morris,[3,36,37,28] Pentti J. Tienari,[9,28] and Bryan J. Traynor[2,14,38,*]

[1]Neuromuscular Diseases Research Unit, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892, USA


2011

# *C9orf72*: the history

# *C9orf72* GENETIC EXPANSION




The *C9orf72* repeat expansion and possible mechanisms to cause frontotemporal dementia-motor neuron disease.

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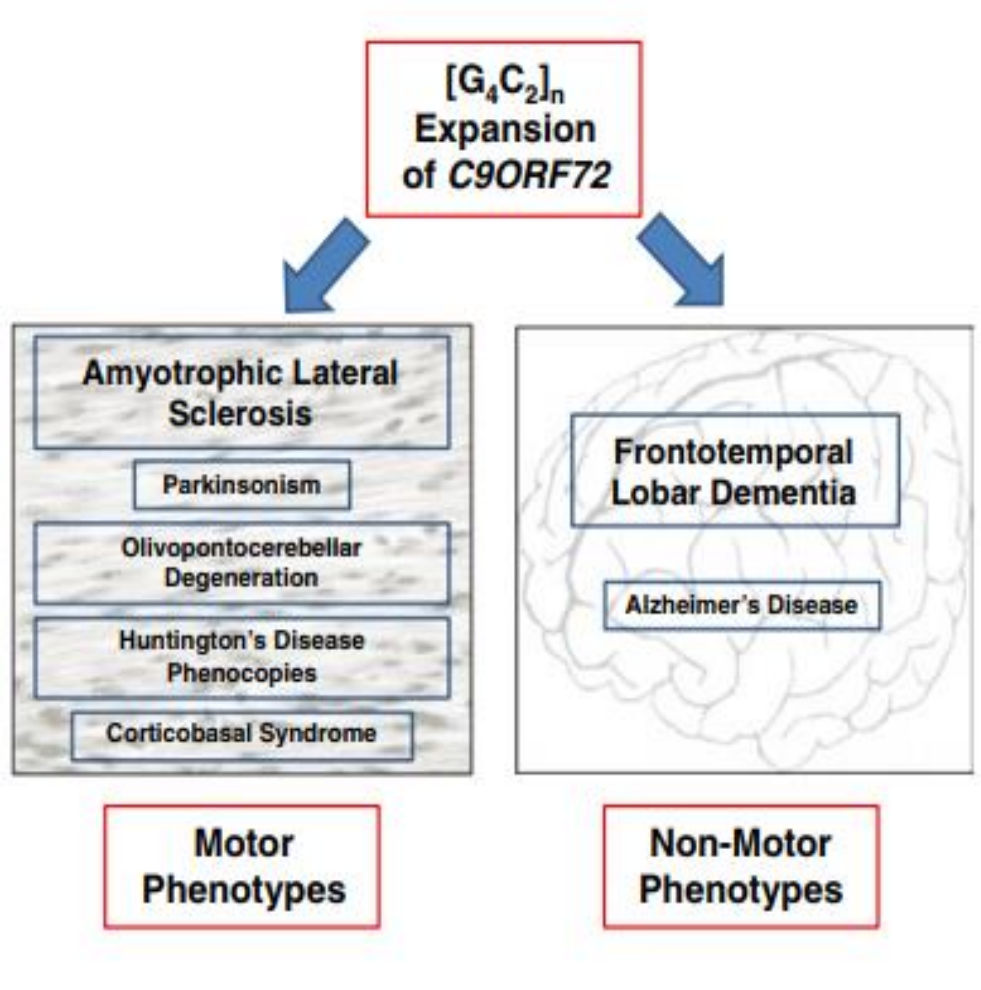
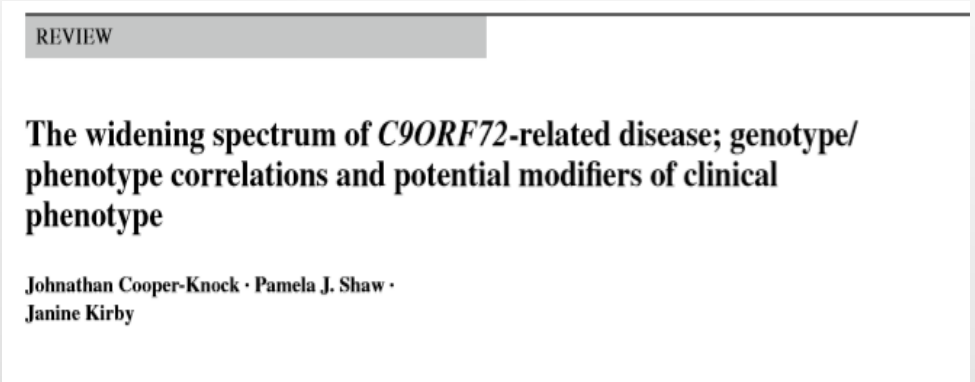
# C9orf72 genetic expansion: clinical presentation




Acta Neuropathol (2014)



REVIEW

**The widening spectrum of *C9ORF72*-related disease; genotype/ phenotype correlations and potential modifiers of clinical phenotype**

Johnathan Cooper-Knock · Pamela J. Shaw · Janine Kirby

**Variabillity in clinical presentation and prognosis**

The repeat expansion has been associated with several different clinical syndromes including a Huntington-like presentation, Alzheimer's disease, ataxia, and even psychiatric illness.

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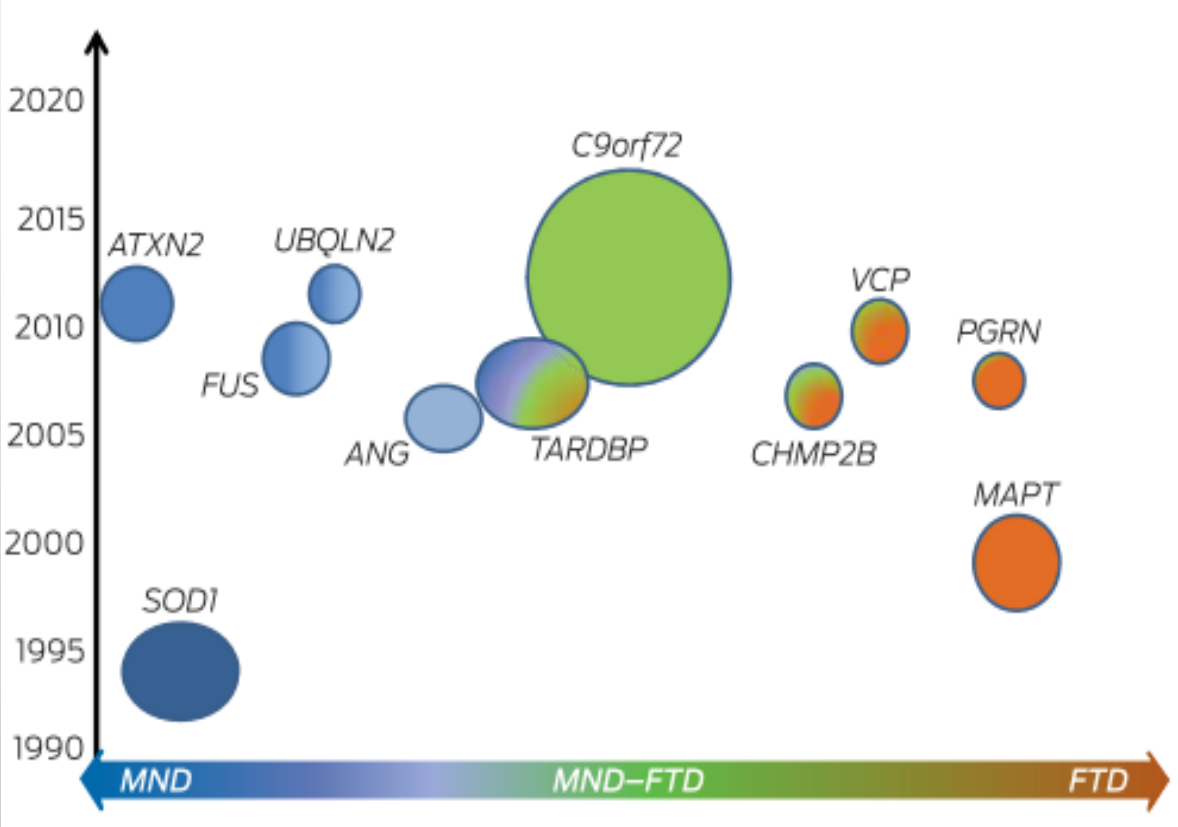
# GENETICS UNDERLYING THE ALS-FTD CONTINUUM




Motor neuron disease: progress and challenges. T. Dharmadasa et al. [2017]

**Neurogenetics** has contributed significant evidence for an **overlap** between ALS and FTD.

Different **genes** are now linked to disease across the **ALS-FDT spectrum**, although many of these are primarily associated with FTD or MND only, with some accounting for only a handful of cases.

# GENETICS UNDERLYING THE ALS-FTD CONTINUUM (2)

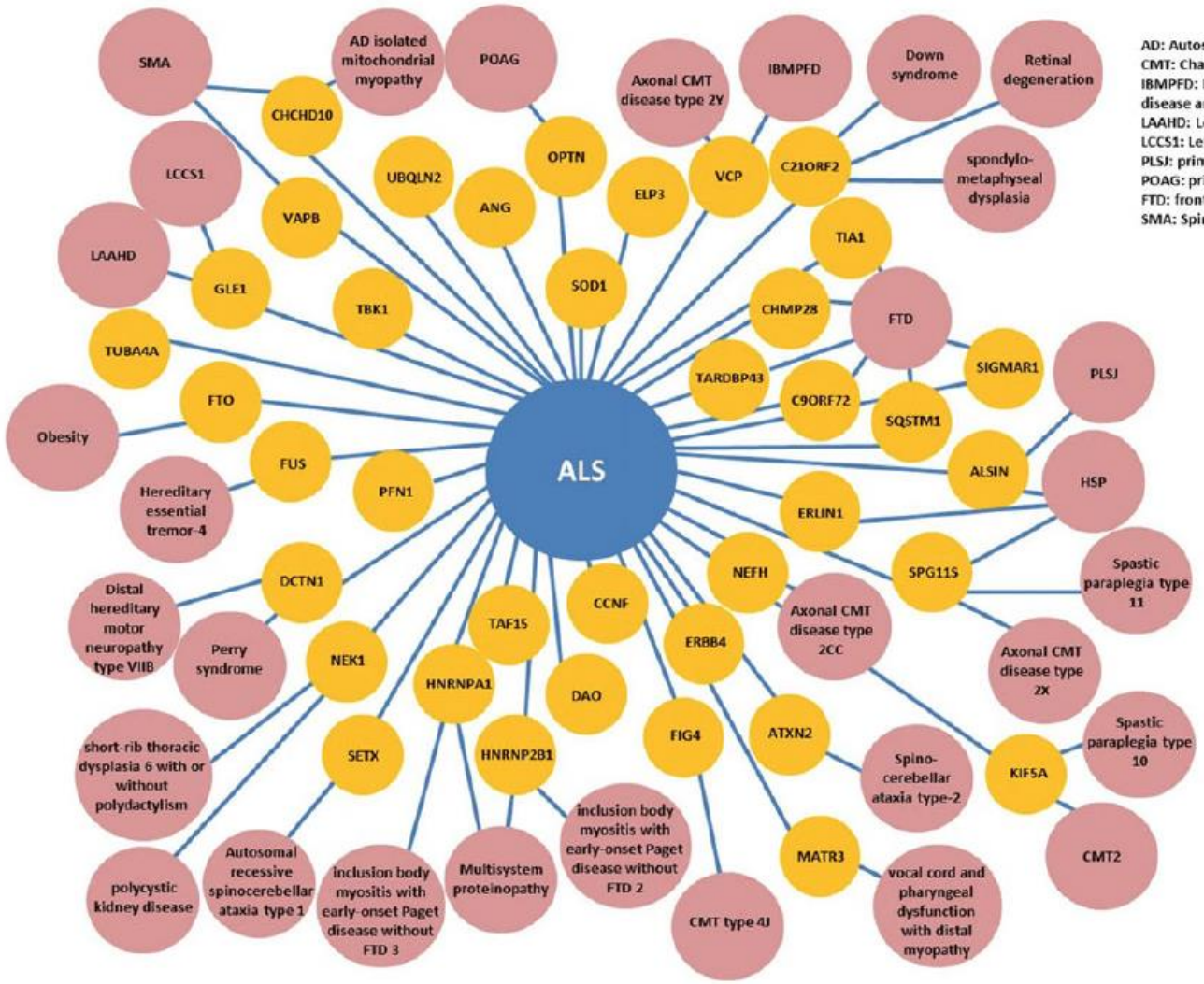
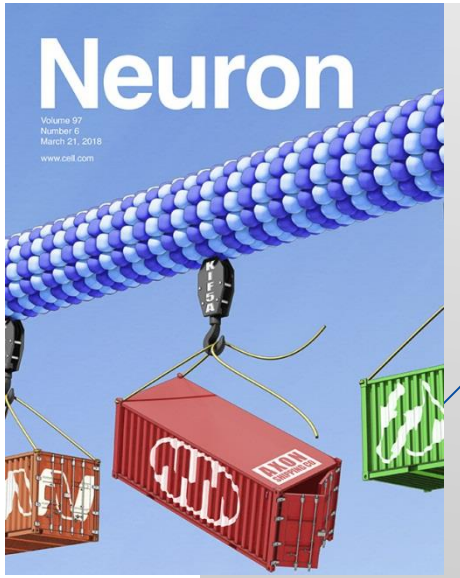



**FIGURE 1** The ALS-associated diseasome

**Genome-wide Analyses Identify KIF5A as a Novel ALS Gene**

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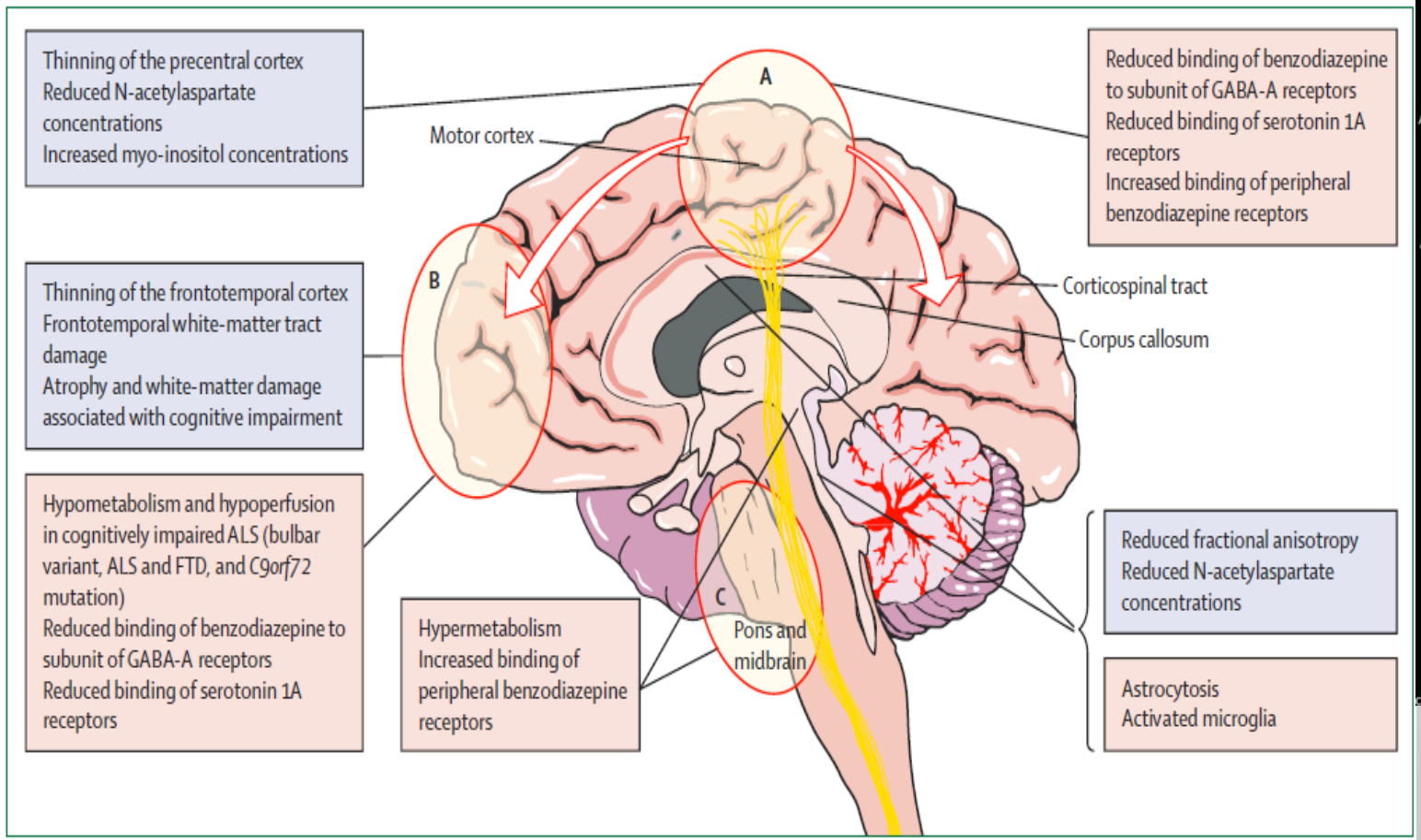
# THE ROLE OF NEUROIMAGING

## Neuroimaging in amyotrophic lateral sclerosis: insights into structural and functional changes

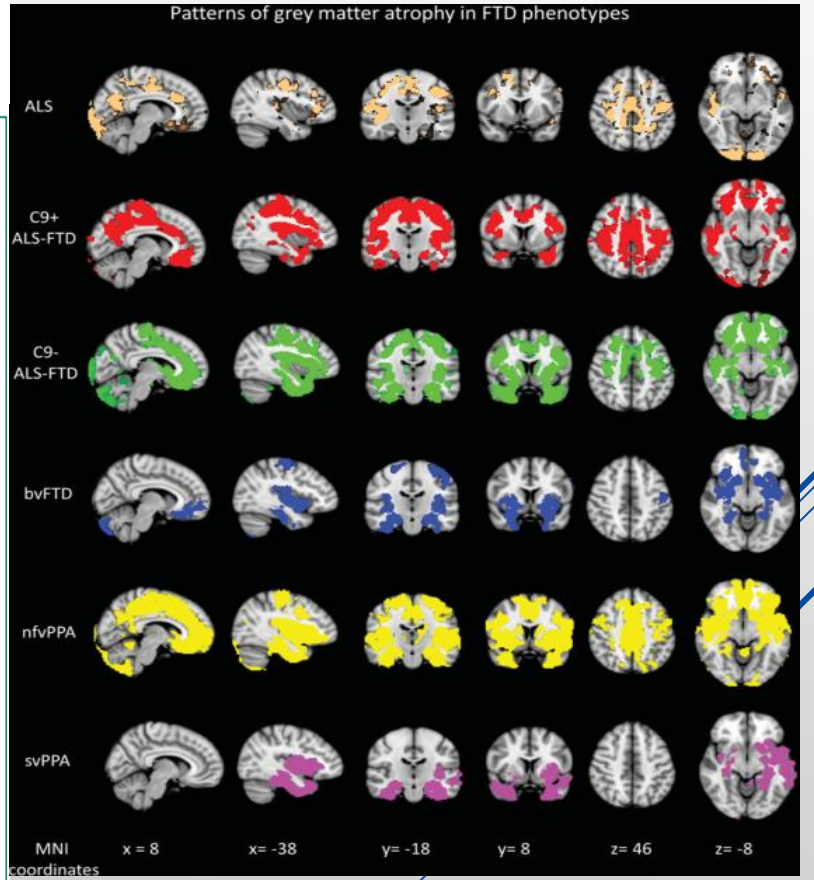
*Adriano Chiò*, Marco Pagani*, Federica Agosta, Andrea Calvo, Angelina Cistaro, Massimo Filippi**

*Lancet Neurol* 2014; 13: 1228–40

In the past two decades, structural and functional neuroimaging findings have greatly modified longstanding notions




Neuroimaging patterns along the ALS-FTD spectrum: a multiparametric imaging study (2017)

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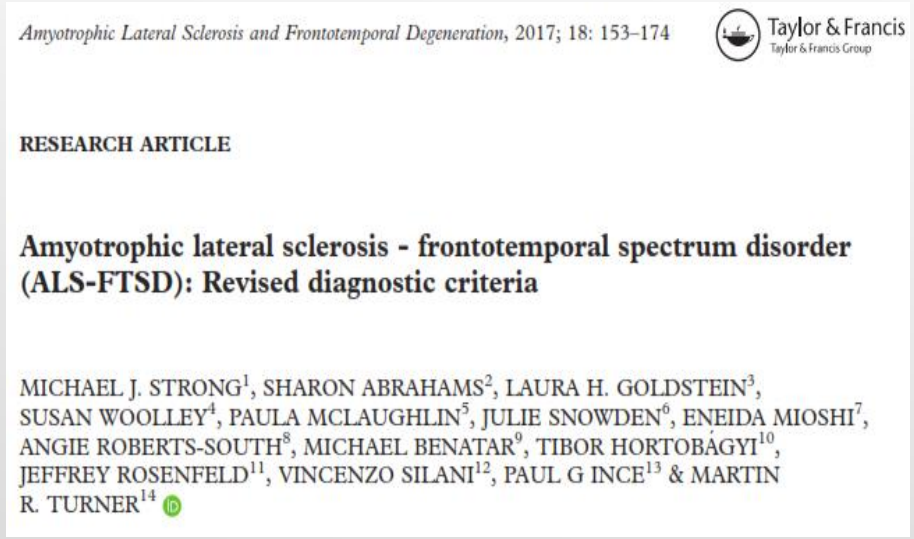
# DIAGNOSIS



*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2017; 18: 153–174

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

**Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria**

MICHAEL J. STRONG[1], SHARON ABRAHAMS[2], LAURA H. GOLDSTEIN[3], SUSAN WOOLLEY[4], PAULA MCLAUGHLIN[5], JULIE SNOWDEN[6], ENEIDA MIOSHI[7], ANGIE ROBERTS-SOUTH[8], MICHAEL BENATAR[9], TIBOR HORTOBÁGYI[10], JEFFREY ROSENFELD[11], VINCENZO SILANI[12], PAUL G INCE[13] & MARTIN R. TURNER[14]

*AXIS 1 – Defining the motor neuron disease variant*

*AXIS 2 – Defining the neuropsychological deficits*

*AXIS 3 – Additional  non-motor disease manifestation*

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# DIAGNOSIS (2)

*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2016; 1–10

Taylor & Francis
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RESEARCH ARTICLE

## The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

BARBARA POLETTI[1]*, FEDERICA SOLCA[1]*, LAURA CARELLI[1], FABIANA MADOTTO[2], ANNALISA LAFRONZA[1], ANDREA FAINI[3], ALESSIA MONTI[4], STEFANO ZAGO[5], DANIELA CALINI[1], CINZIA TILOCA[1], ALBERTO DORETTI[1,6], FEDERICO VERDE[1,6], ANTONIA RATTI[1,6], NICOLA TICOZZI[1,6], SHARON ABRAHAMS[7]* & VINCENZO SILANI[1,6]*

Cognitive screening tests specific to motor neuron disease have been developed.

**ECAS** assesses several cognitive domains including executive function, verbal fluency, language, and visuospatial function.

**EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN – ECAS**

**Versione Italiana - Poletti et al. (2016)**

Data dell'esame: .....
Anni di scolarità: .....
Professione: .....
.....
Lateralità manuale: .....

Nome: .....
Data di nascita: .....
Indirizzo e numero di telefono: .....
.....
.....

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# CONCLUSIONS

- **ALS** is now considered to be a **multisystem disorder** encompassing motor, cognitive and behavioral changes.

- The last decade has seen rapid developments across the genetic, clinical and pathophysiological mechanisms in the **ALS-FTD continuum**.

- The identification of ***C9orf72*** has challenge the concept of ALS and FTD as a single disease entities by explaining the genetic link between the conditions. A striking characteristic of disease associated with C9ORF72 repeat expansion is large **variability** in clinical presentation and prognosis: the reason of this fact is unknown.

- It is essential to better delineate the **underlying molecular pathogenesis** of these diseases in order to find an effective therapy. **Ongoing drug trials** taget at pathology, genetic and immunological process offer hope for the future in ALS-FTD.

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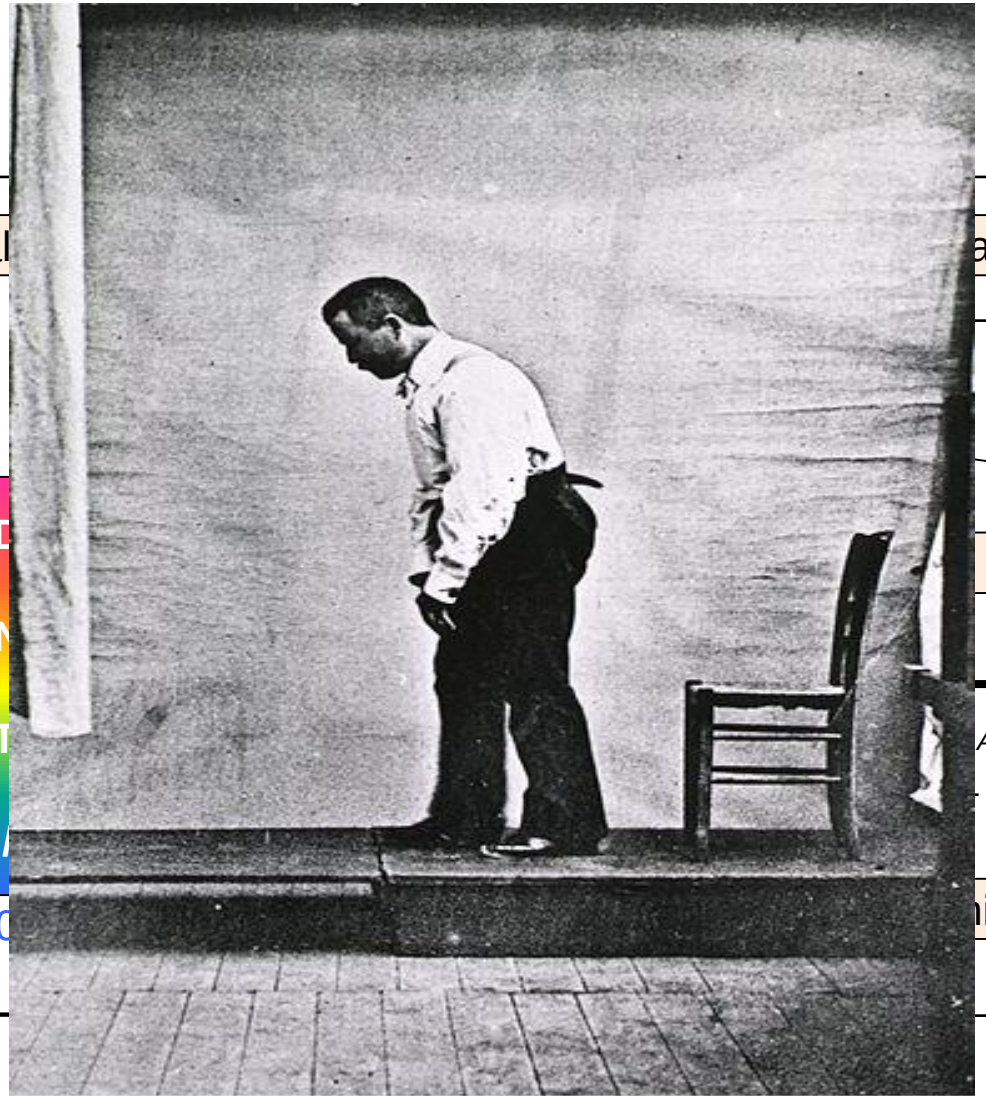
# ALS-FTD: clinical continuum

10%

10%



social

bvFTD

FTD-MN

ALS-FT

ALS-bi

40

anguage

*fluent*

SD

lvPPA



*ALS-SD*

itive impairment

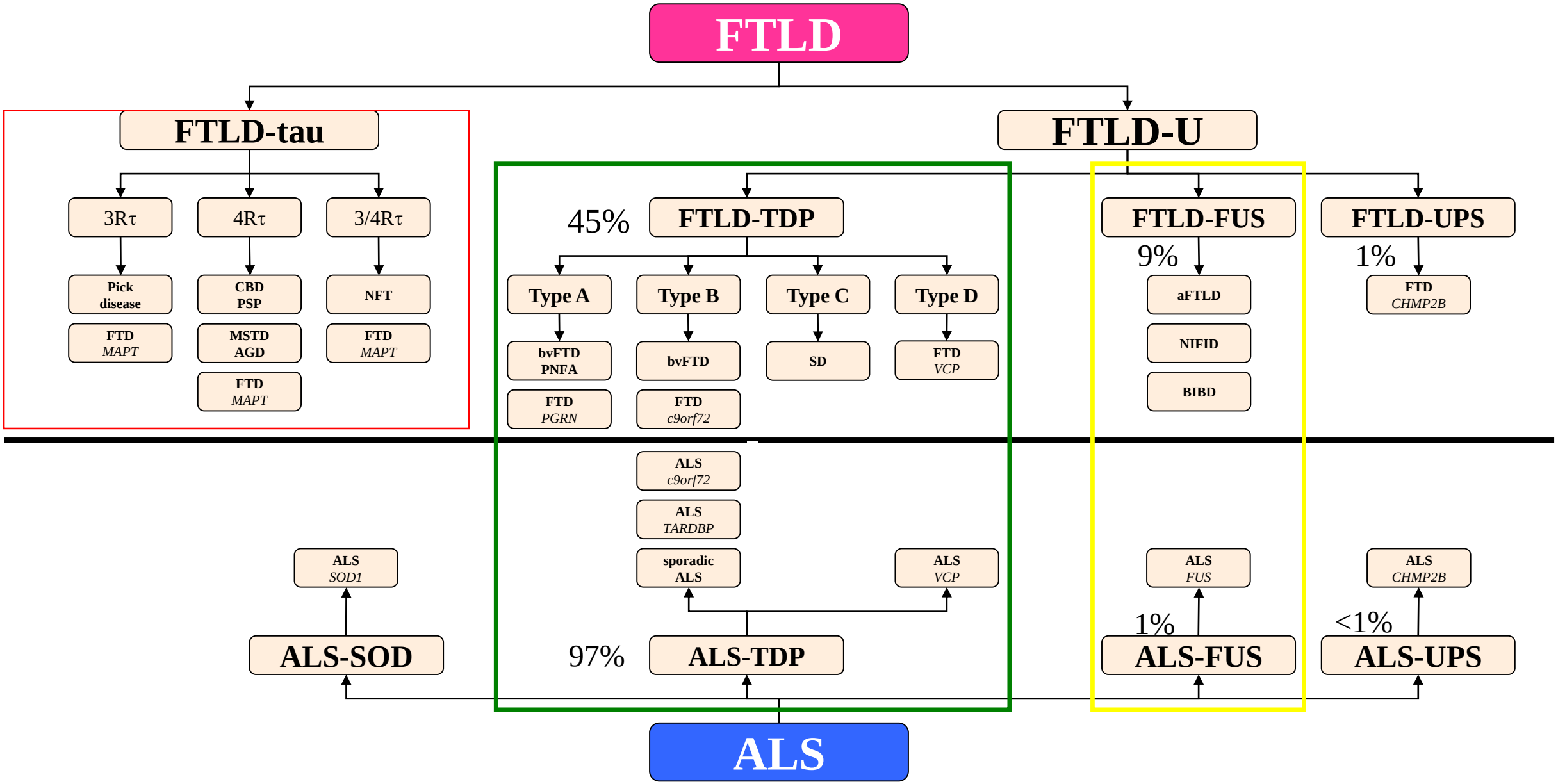
60%

PMA

Other Movement Disorders

PLS

# ALS-FTD: neuropathological continuum

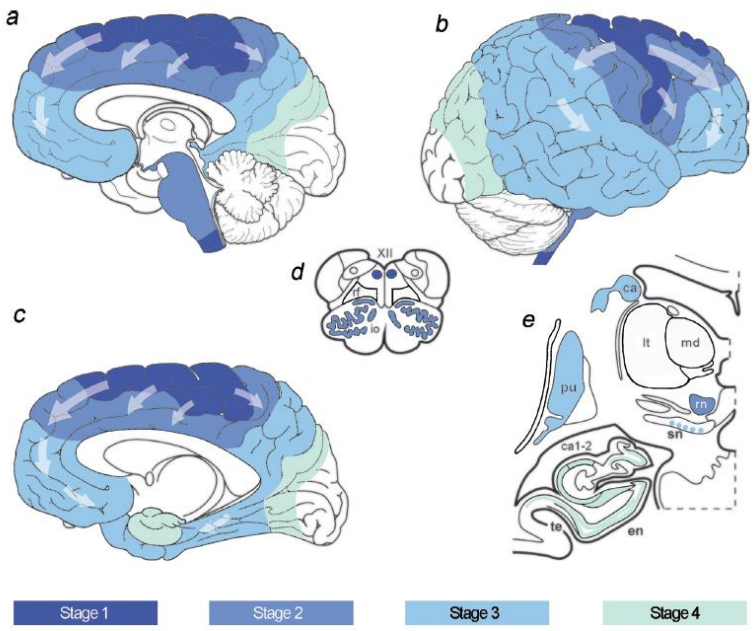


# The real issue

TDP-43 specific encephalopathy

↕

cognitive/behavioral impairment




TDP43 as biomarker

Verde et al., 2017

doi:10.1093/brain/awz099 BRAIN 2019: 0; 1–25 | 1

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A JOURNAL OF NEUROLOGY

REVIEW

# Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

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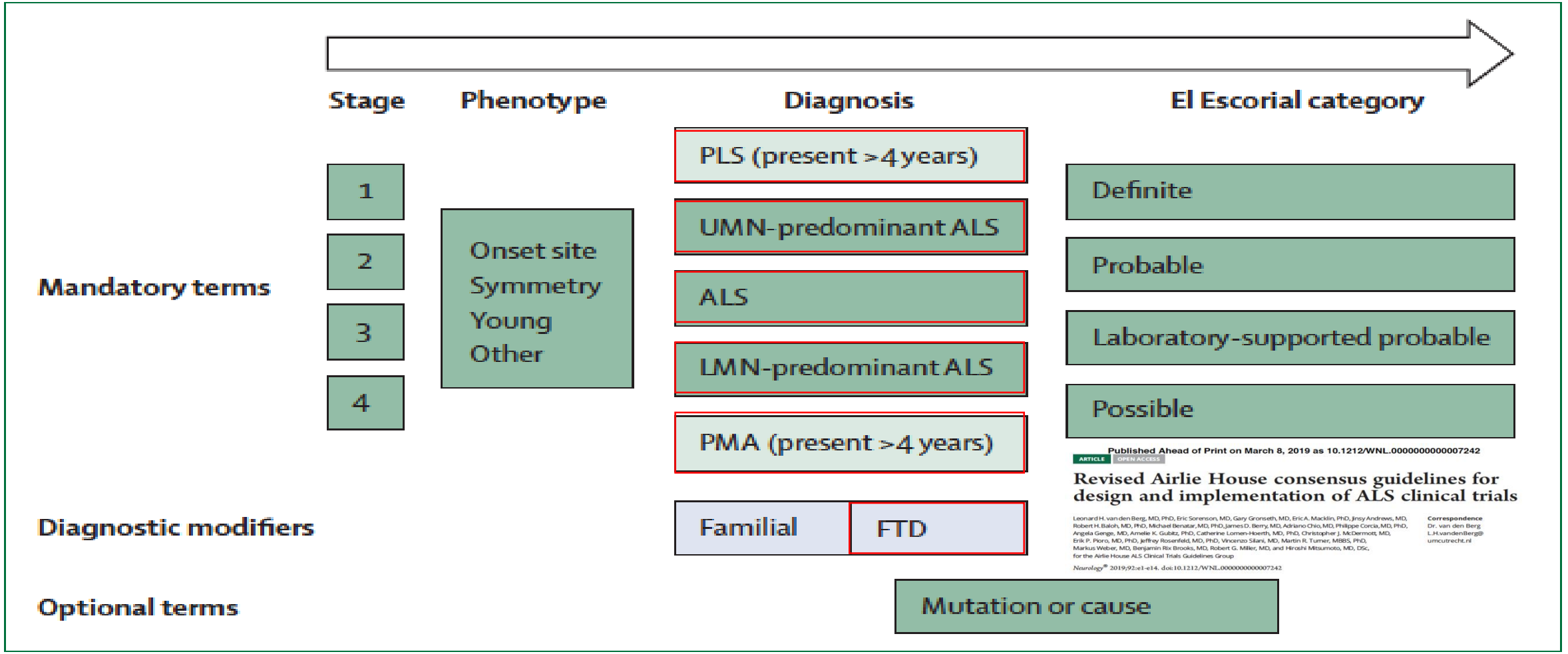
## Box 1 LATE and LATE-NC summary points

- LATE-NC features
  - A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
    - Stage 1: amygdala only
    - Stage 2: +hippocampus
    - Stage 3: +middle frontal gyrus
  - Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC
- LATE-NC is present in >20% (up to 50%) of individuals past age 80 years according to large community-based autopsy series
- LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome ('dementia of the Alzheimer's type')
- The overall public health impact of LATE is on the same order of magnitude as Alzheimer's disease neuropathological changes; the diseases are often comorbid, but which pathology is more severe varies greatly between individuals
- Genetic risk factors for LATE have some overlap with FTLD-TDP and with Alzheimer's disease
- There is no molecule-specific biomarker for LATE. This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer's disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE

# ALS-FTD: new classification ?

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**Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials**

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Al-Chalabi et al., 2016