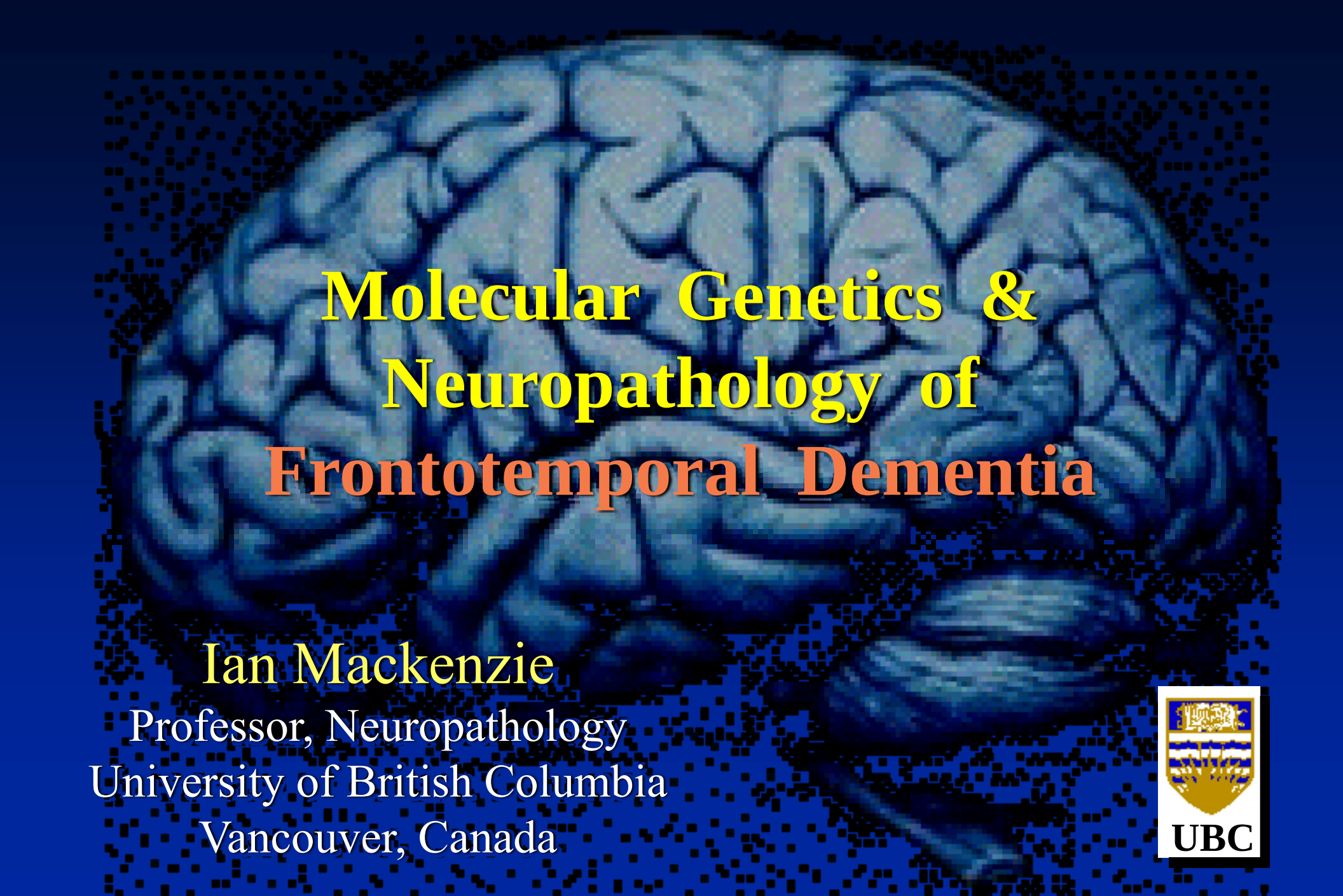


Molecular Genetics & Neuropathology of Frontotemporal Dementia

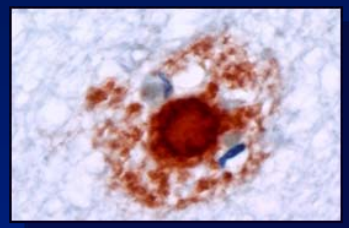
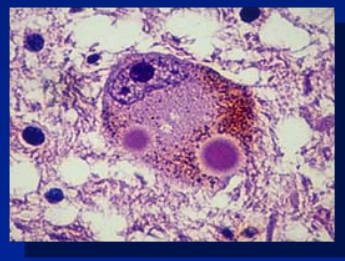
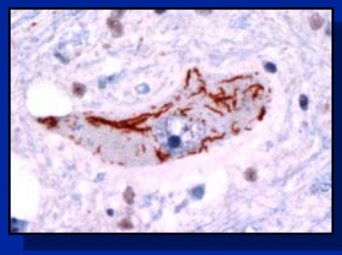
Ian Mackenzie
Professor, Neuropathology
University of British Columbia
Vancouver, Canada

UBC

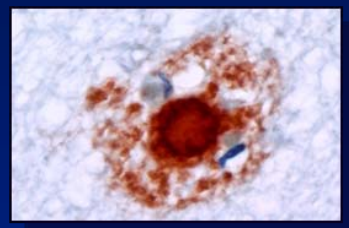
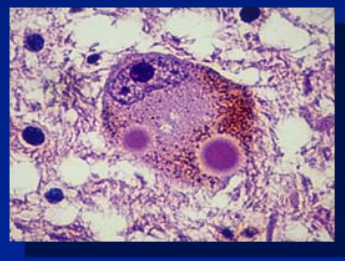
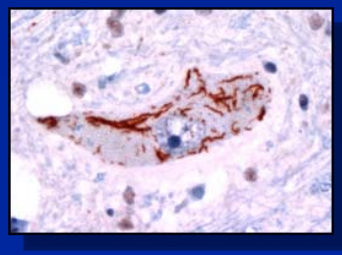
Neurodegenerative diseases

- slow, progressive, permanent loss of neurologic function.
- cause unknown.
- sporadic, familial or inherited.
- degeneration of specific brain region → clinical syndrome.
- pathology: abnormal accumulation of disease specific protein.

Neurodegenerative diseases

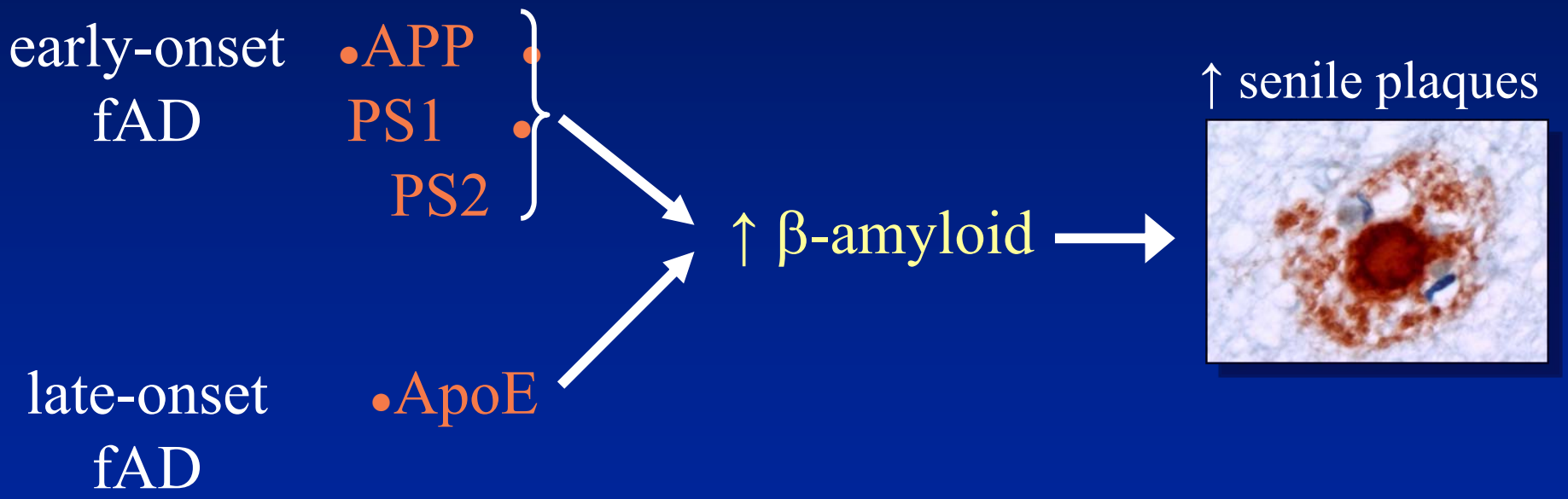
disease	protein deposits	anatomy	clinical
Alzheimer's disease	β-amyloid (senile plaques) 	cerebral cortex	dementia
Parkinson's disease	α-synuclein (Lewy bodies) 	brainstem & basal ganglia	movement disorder
ALS	TDP-43 (skeins) 	spinal cord	weakness

Neurodegenerative diseases

disease	protein deposits	anatomy	clinical
Alzheimer's disease	β-amyloid (senile plaques) 	cerebral cortex	dementia
Parkinson's disease	α-synuclein (Lewy bodies) 	brainstem & basal ganglia	movement disorder
ALS	TDP-43 (skeins) 	spinal cord	weakness

Neurodegenerative diseases

disease	gene	biochemistry	protein deposits

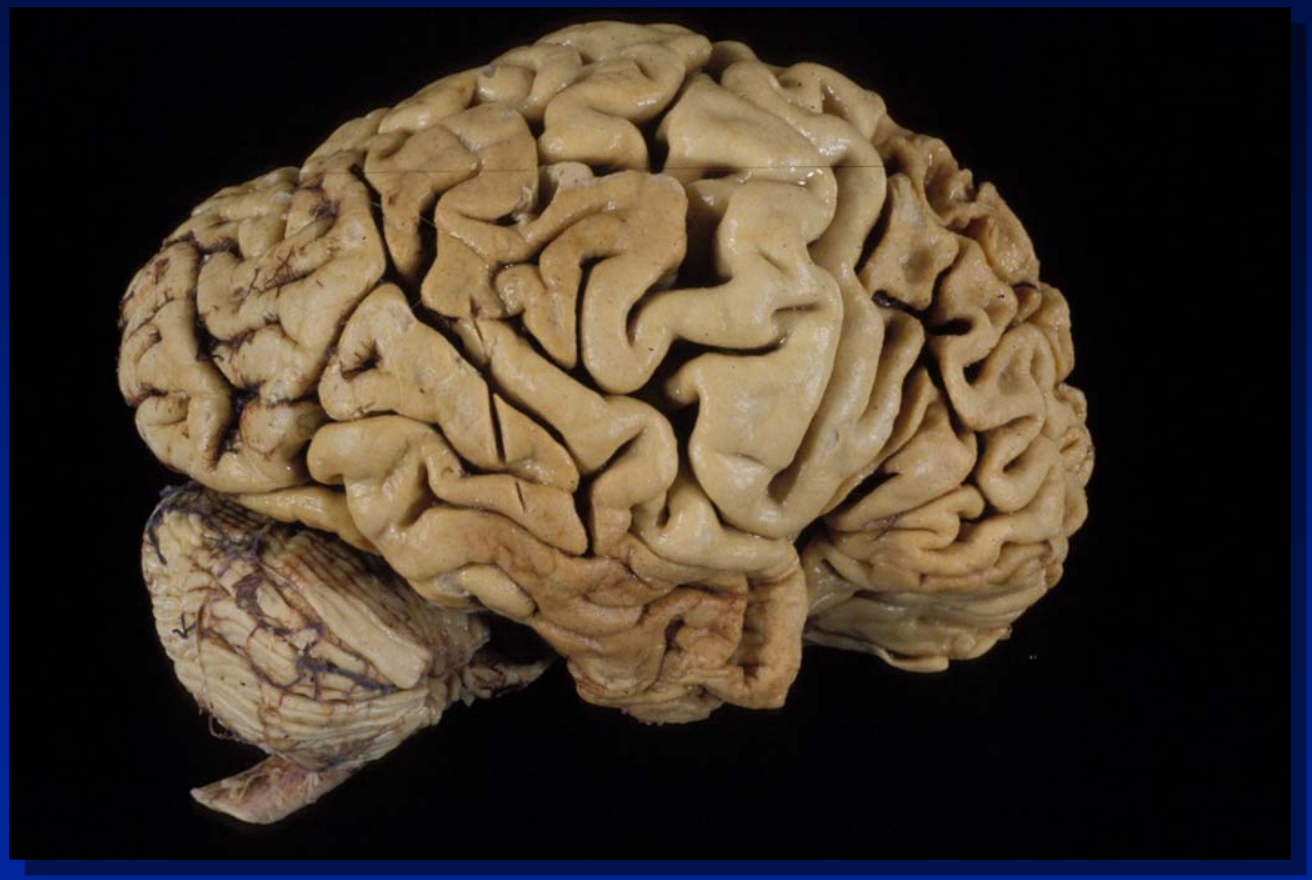


Frontotemporal dementia (FTD)

Clinical syndrome:

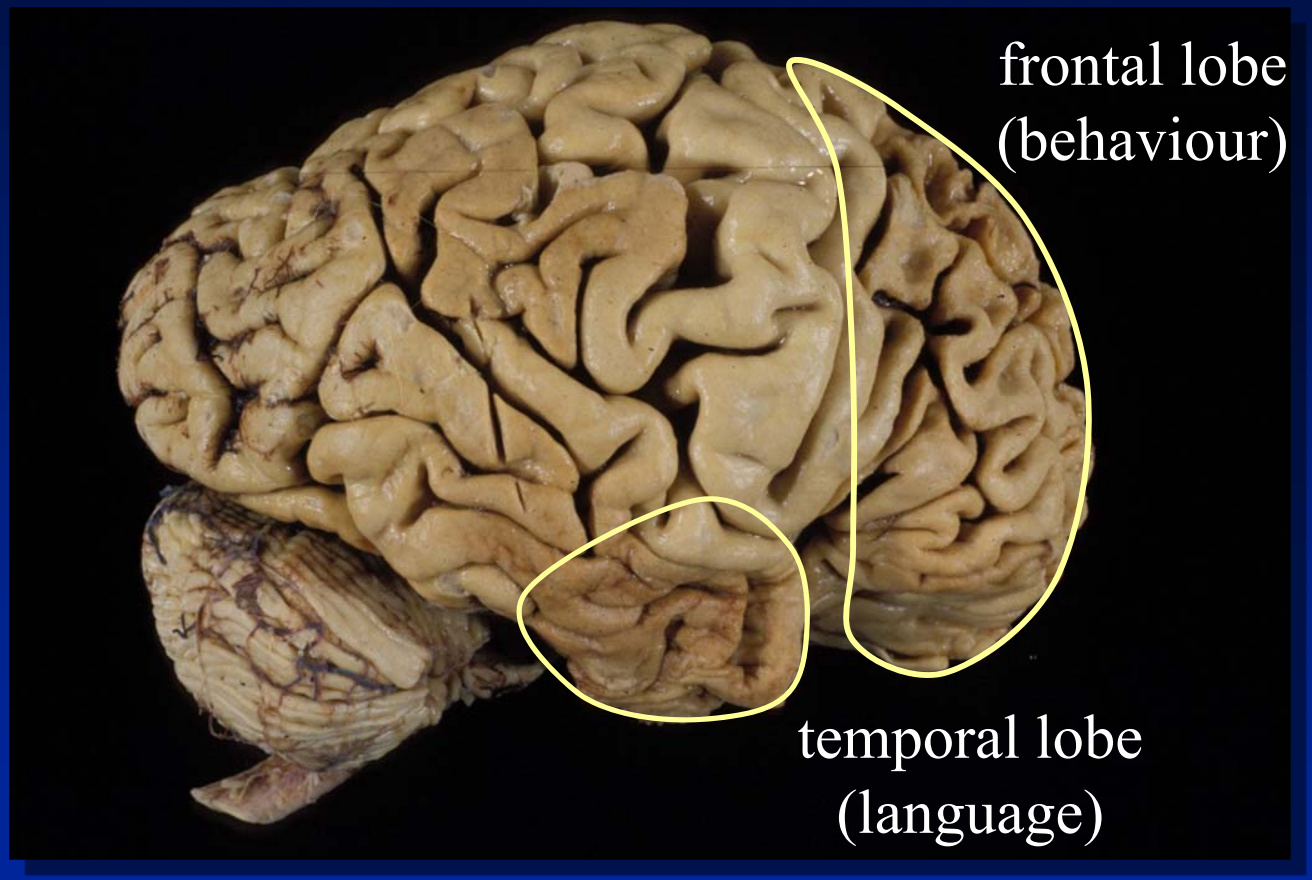
- progressive change in behaviour, personality and/or language.
- often associated with movement disorder (parkinsonism or ALS).
- 25-50% have family history, most autosomal dominant.

Neuropathology of FTD



- selective atrophy of frontal & temporal lobes

Neuropathology of FTD



- selective atrophy of frontal & temporal lobes

Neuropathology of FTD

Microscopic pathology:

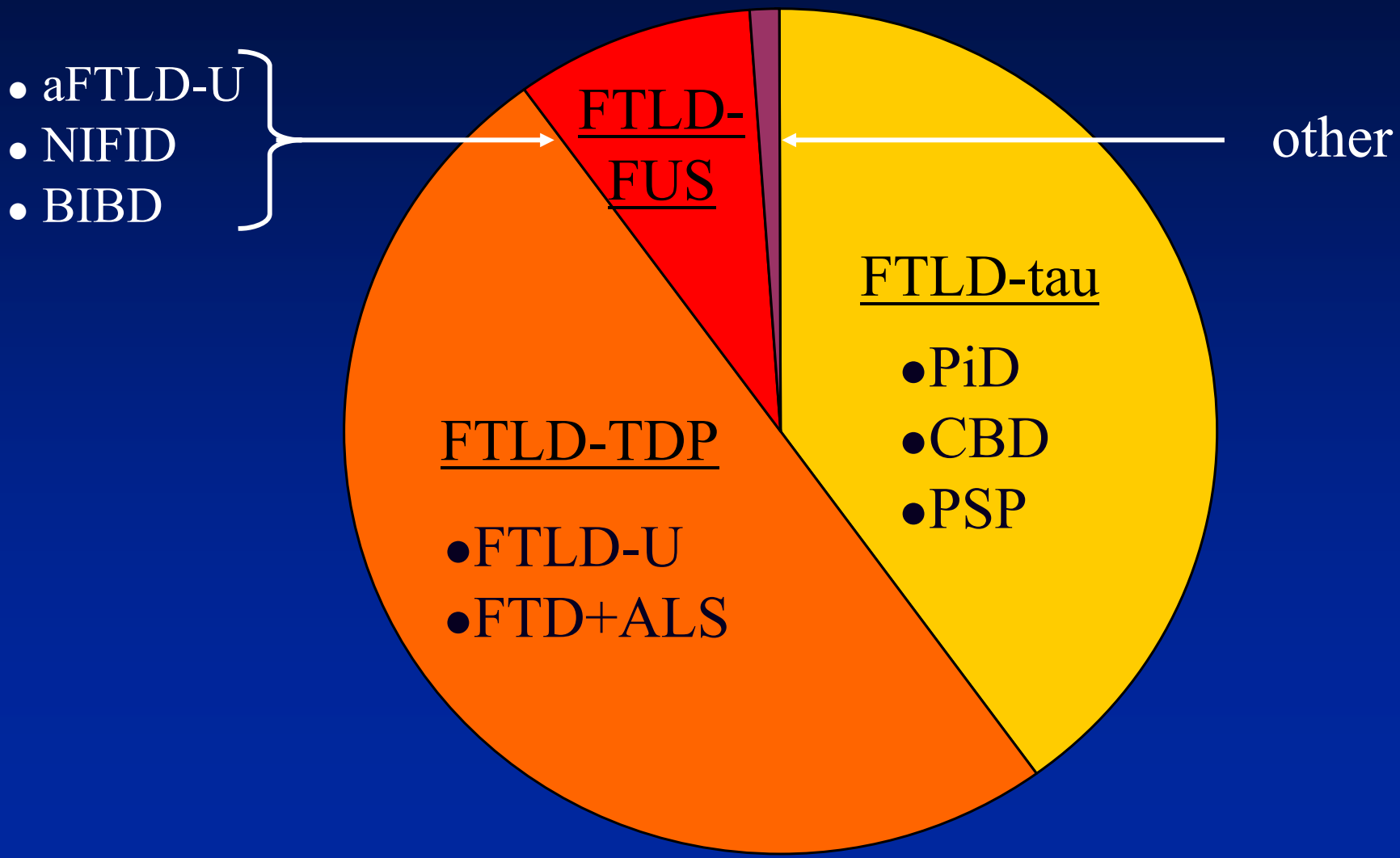
- Pick's disease
- corticobasal degeneration (CBD)
- progressive supranuclear palsy (PSP)
- frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U)
- FTD with ALS
- atypical FTLD-U
- neuronal intermediate filament inclusion disease
- basophilic inclusion body disease
- dementia lacking distinctive histopathology (DLDH)

Neuropathology of FTD

Microscopic pathology:

	protein
Pick's disease	tau
corticobasal degeneration (CBD)	tau
progressive supranuclear palsy (PSP)	tau
frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U)	TDP-43
FTD with ALS	TDP-43
atypical FTLD-U	FUS
neuronal intermediate filament inclusion disease	FUS
basophilic inclusion body disease	FUS
dementia lacking distinctive histopathology (DLDH)	none

Neuropathology of FTD

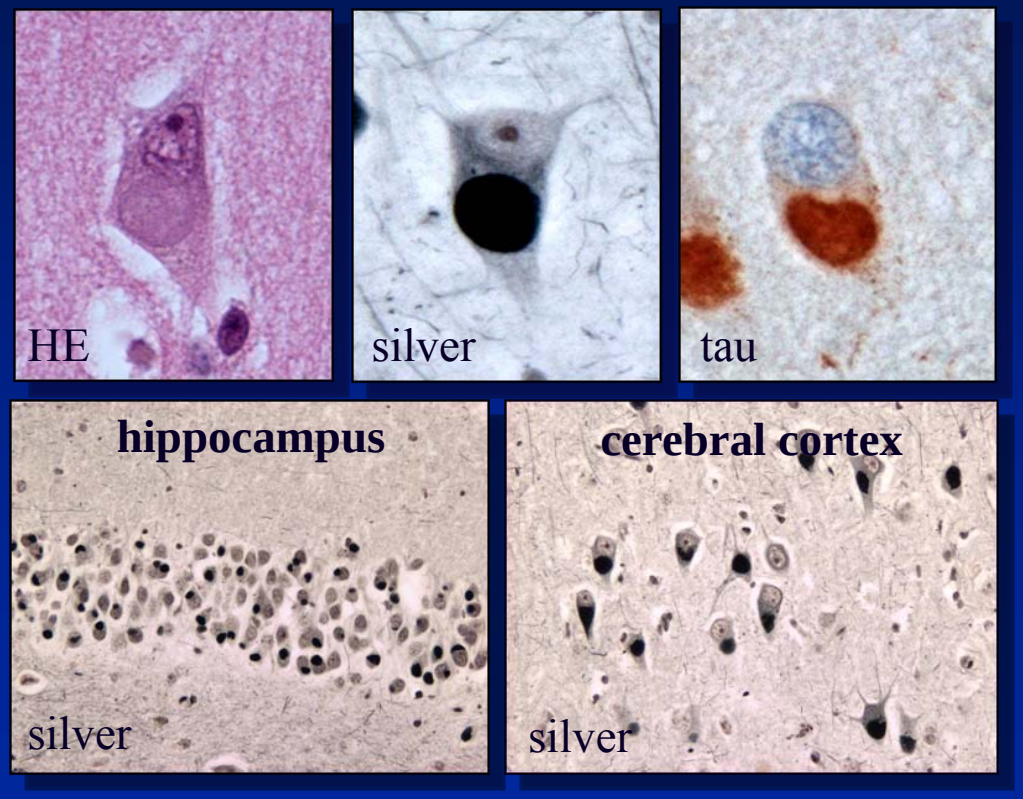


Tau protein

- a microtubule associated protein.
- gene on chromosome 17.
- forms cytoskeleton of neurons, important for axonal transport.
- abnormal tau accumulates in neurons and glial cells (inclusion bodies).

Pick's disease

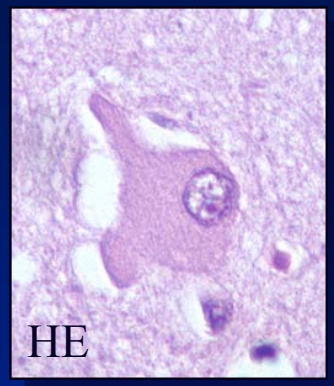
- usually presents as FTD.



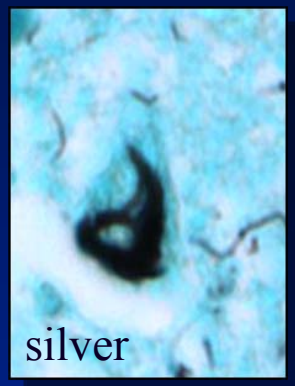
- Pick bodies.

Corticobasal degeneration (CBD)

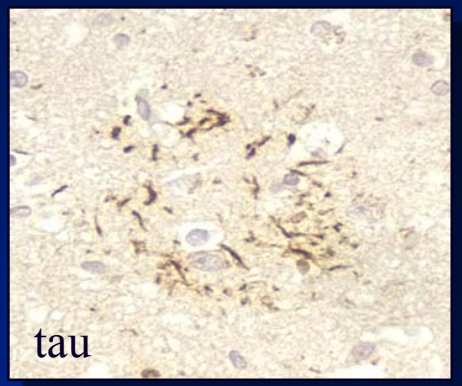
- may present as parkinsonism or FTD.



swollen neuron

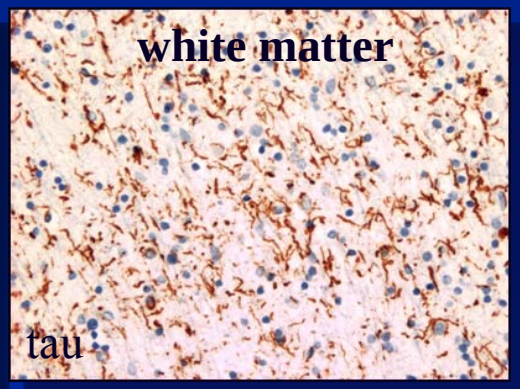


neuronal tangle



astrocytic plaque

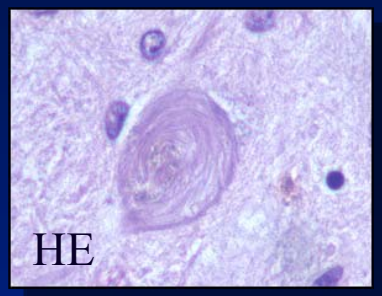
coiled body



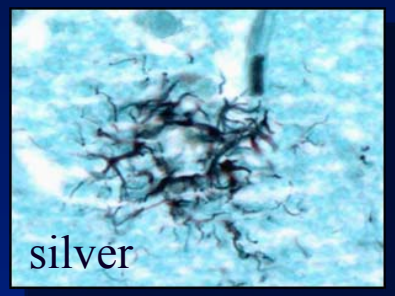
- abnormal accumulation of tau in neurons and glia.
- cortex, subcortical grey and white matter.

Progressive supranuclear palsy (PSP)

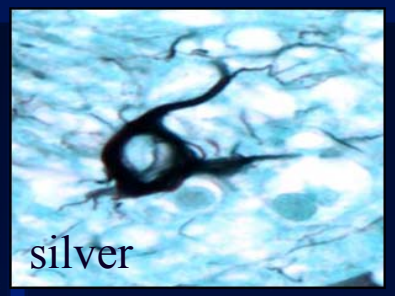
- most often presents as parkinsonism but may cause FTD.



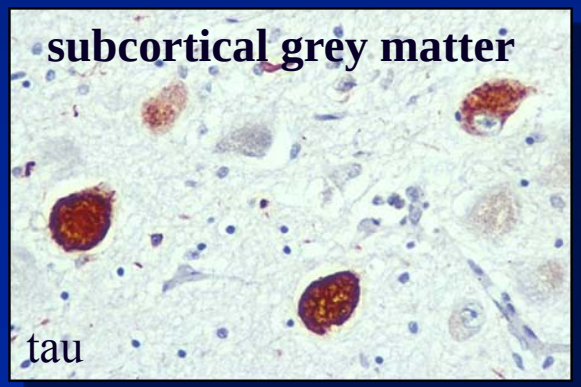
neurofibrillary tangle

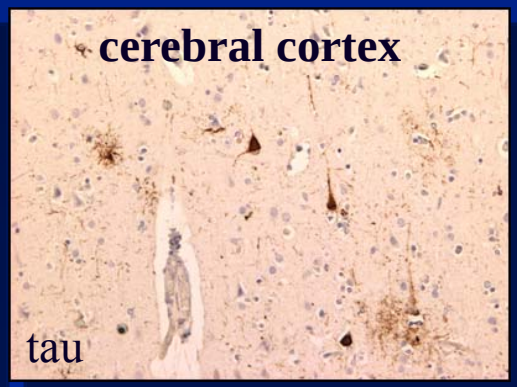


tufted astrocyte



thorny astrocyte

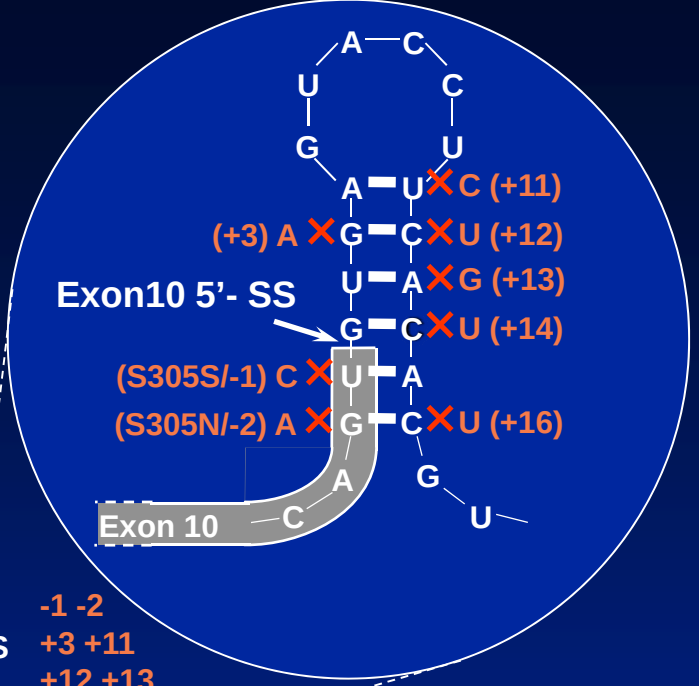




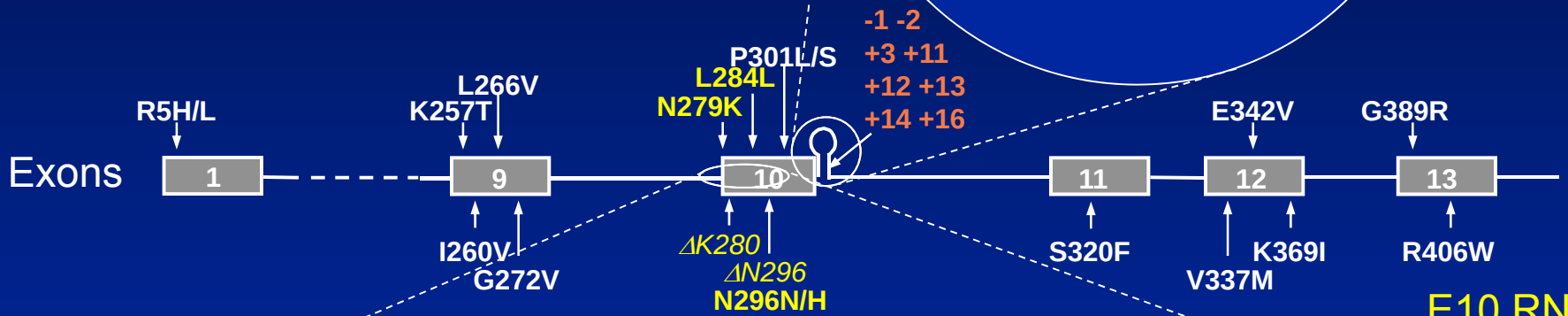
- abnormal accumulation of tau in neurons and glia.
- cortex, subcortical grey and white matter.

MAPT mutations

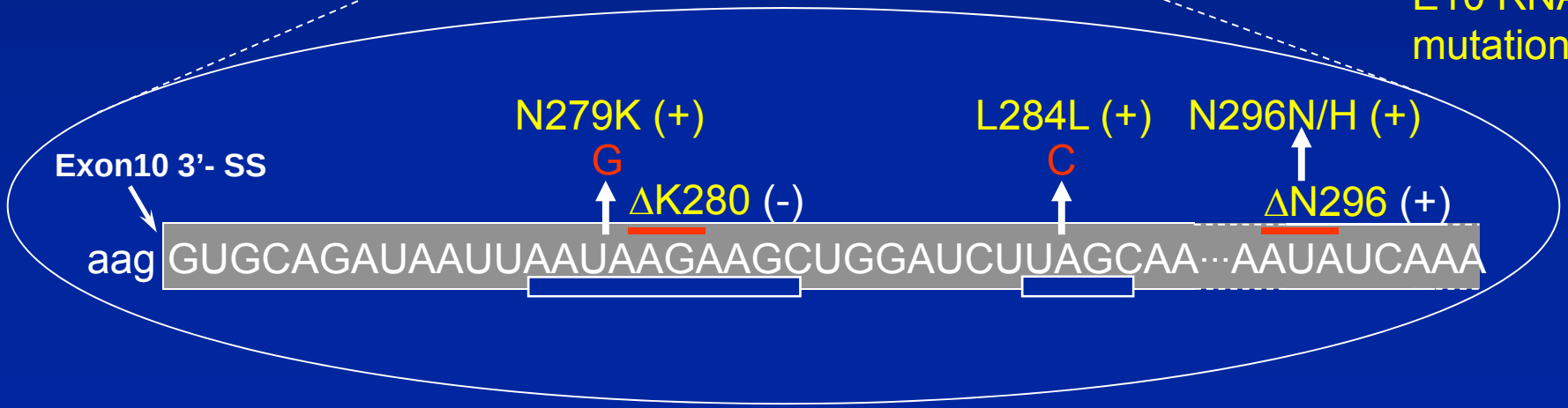
- 44 mutations in >130 families.
- 10-20% familial FTD.
- FTD + parkinsonism.
- FTLD-tau pathology.



E10 RNA splicing mutations (5'SS)



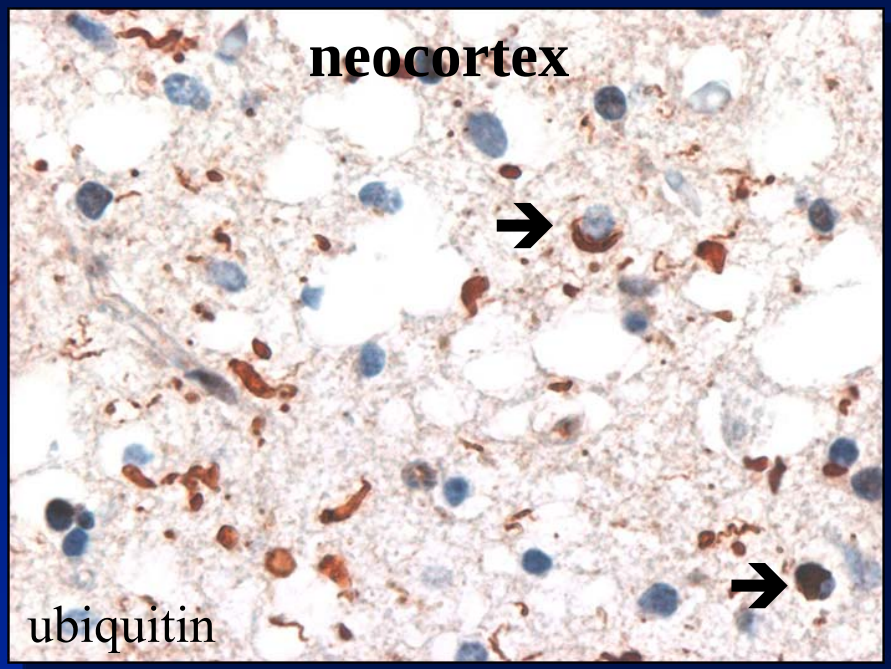
E10 RNA splicing mutations (internal)

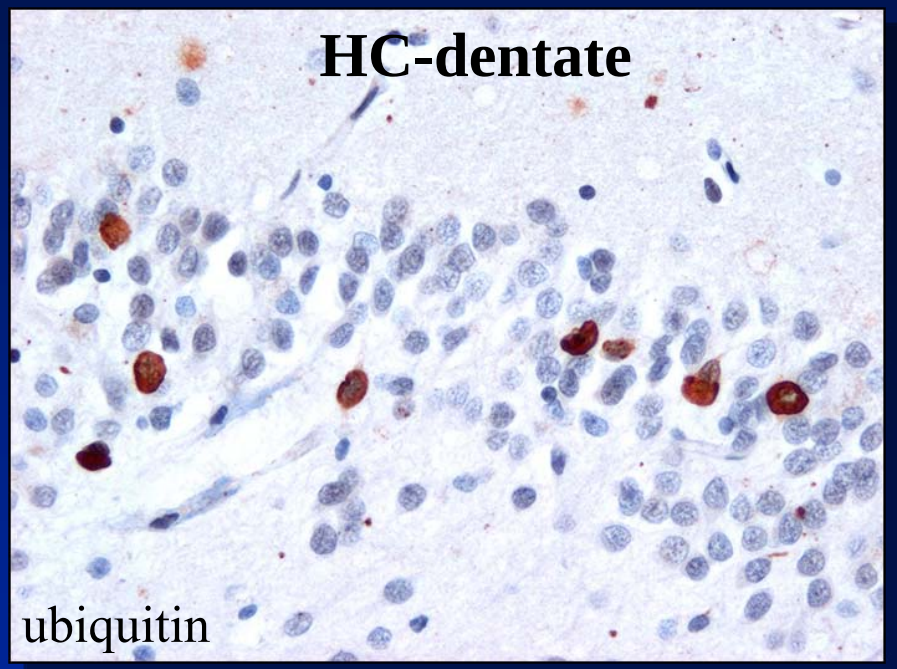


FTLD with ubiquitinated inclusions

- originally identified as cerebral pathology in patients with ALS and dementia.
- now recognized as most common FTD pathology.
- neuronal inclusions only recognized with immunohistochemistry for ubiquitin (non-specific).
- TDP-43 recently identified as abnormal (ubiquitinated) protein in most FTLD-U and ALS.

FTLD-U





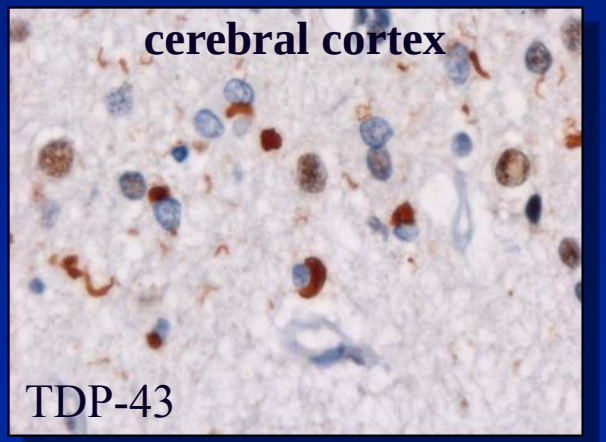
- abnormal protein deposits in neurons.
- stain for ubiquitin but not tau or other proteins.

REPORTS SCIENCE VOL 314 6 OCTOBER 2006

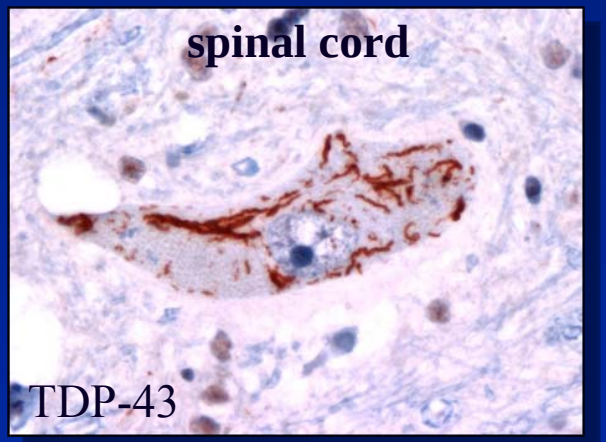
Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

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]†

- nuclear protein involved in mRNA processing.
- abnormally fragments accumulate in neurons and glia.



FTLD-U

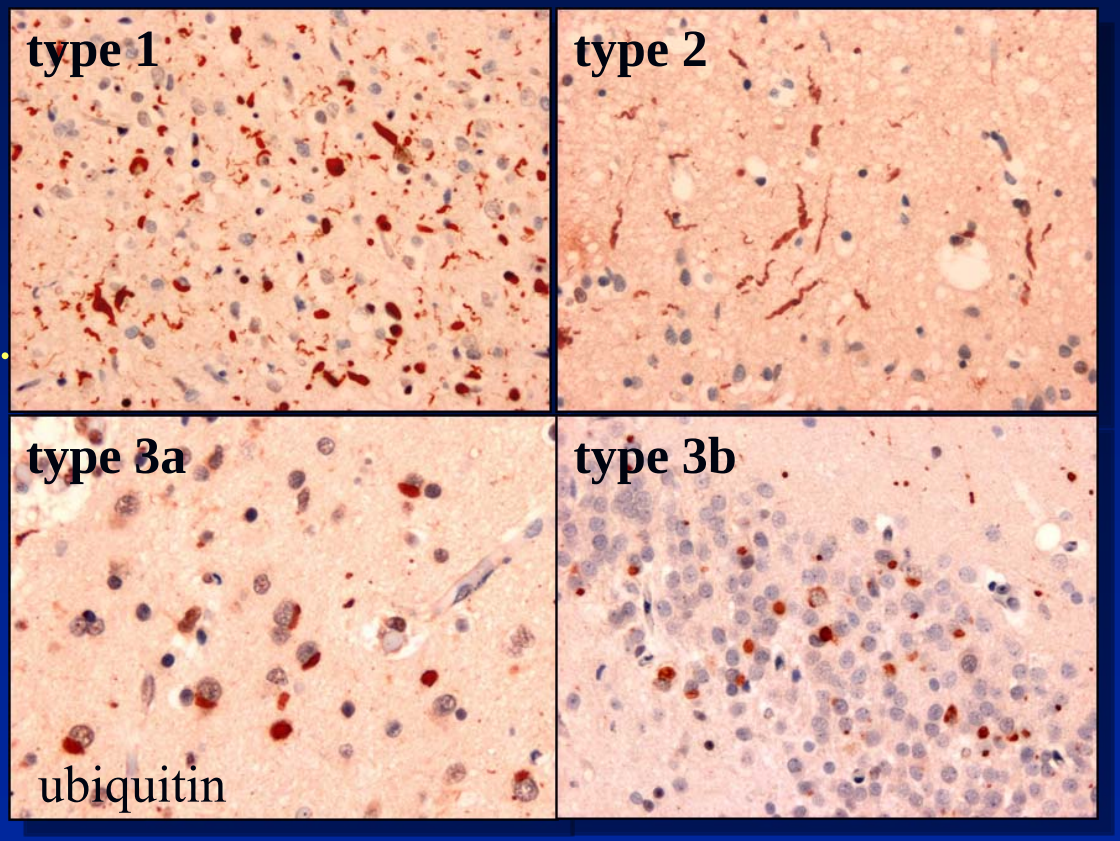


ALS

FTLD-U subtypes

- neurites & NCI in layer II.
- 32%.
- bvFTD or PNFA.

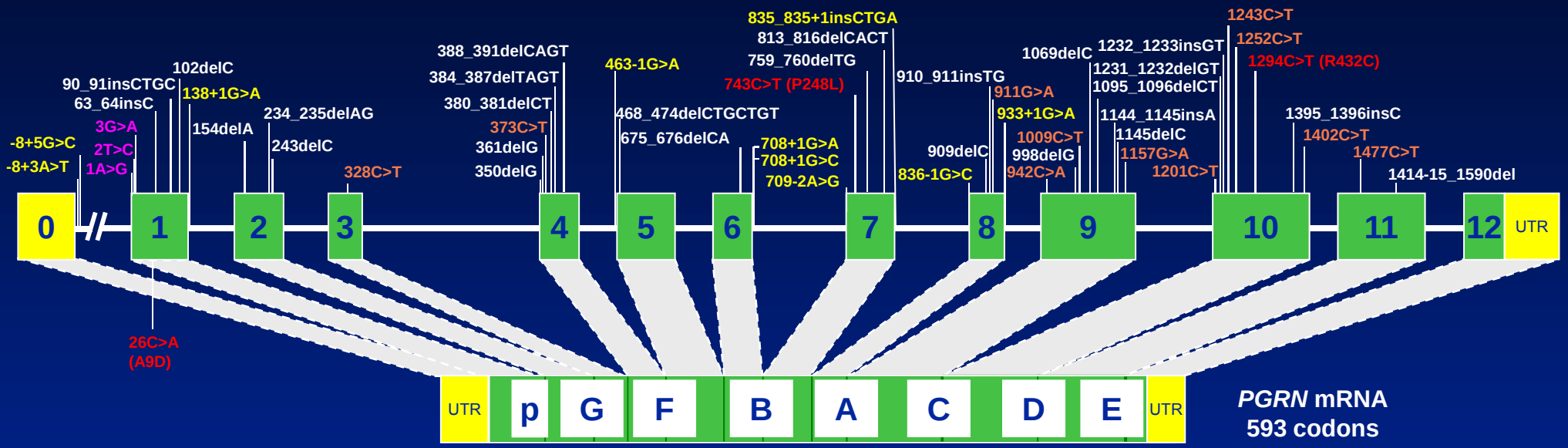
- NCI in neocortex.
- 20%.
- ALS-FTD.



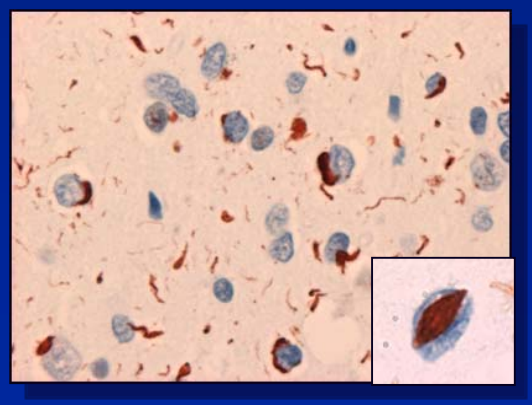
- neurites in layer II.
- 27%.
- SD.

- NCI in HC.
- 22%.
- bvFTD or ALS-FTD.

GRN mutations in FTD



- progranulin = secreted neuronal growth factor.
- *GRN* gene on chromosome 17.
- 68 mutations in 226 families.
- all cause ↓ functional PGRN.
- 12-25% of familial FTD.
- clinical = bvFTD or PPA, no ALS.
- pathology = FTLD-TDP type 1 with neuronal intranuclear inclusions.

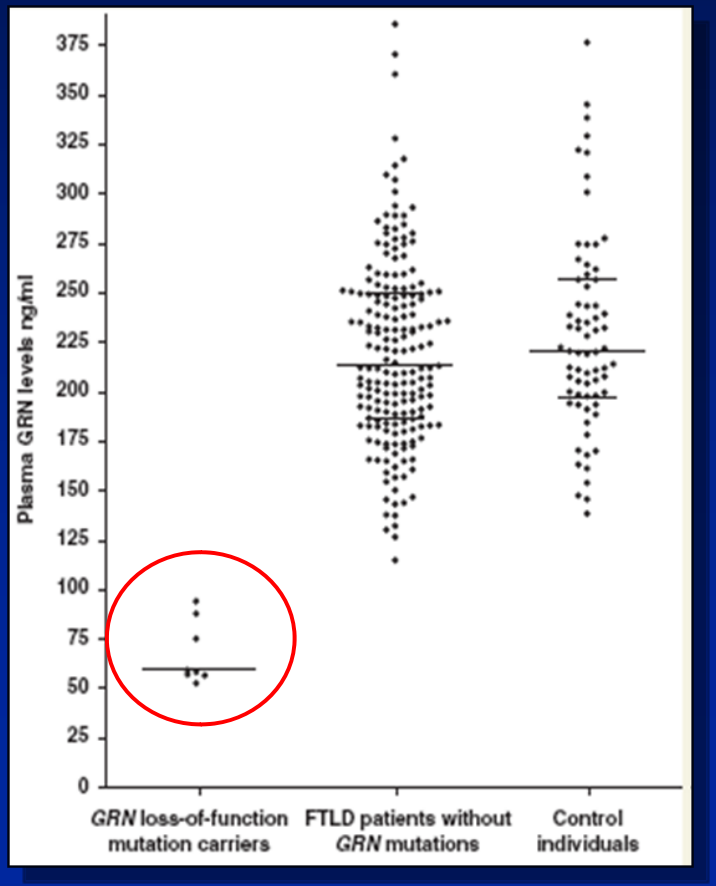


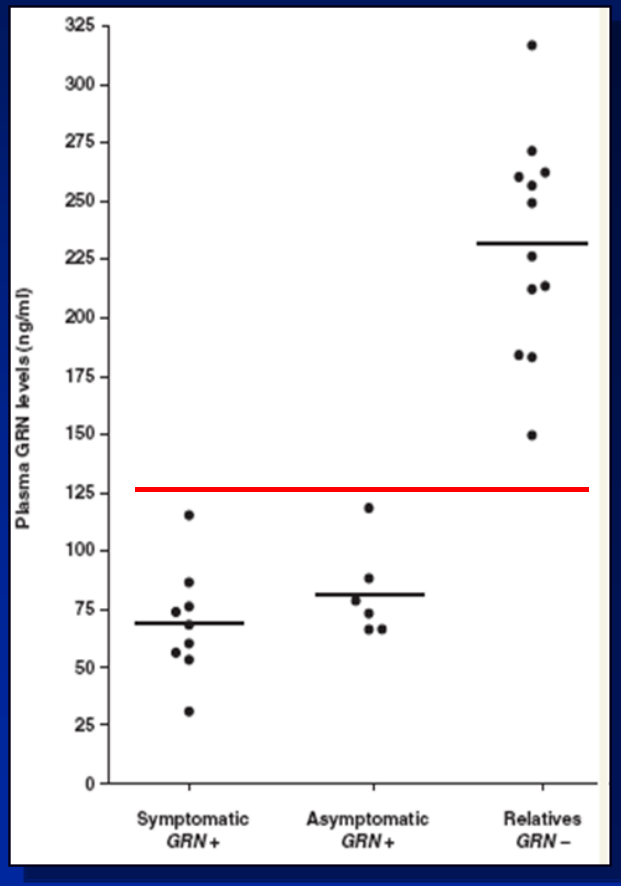
doi:10.1093/brain/awn352 Brain 2009: 132; 583–591 | 583

BRAIN
A JOURNAL OF NEUROLOGY

Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members

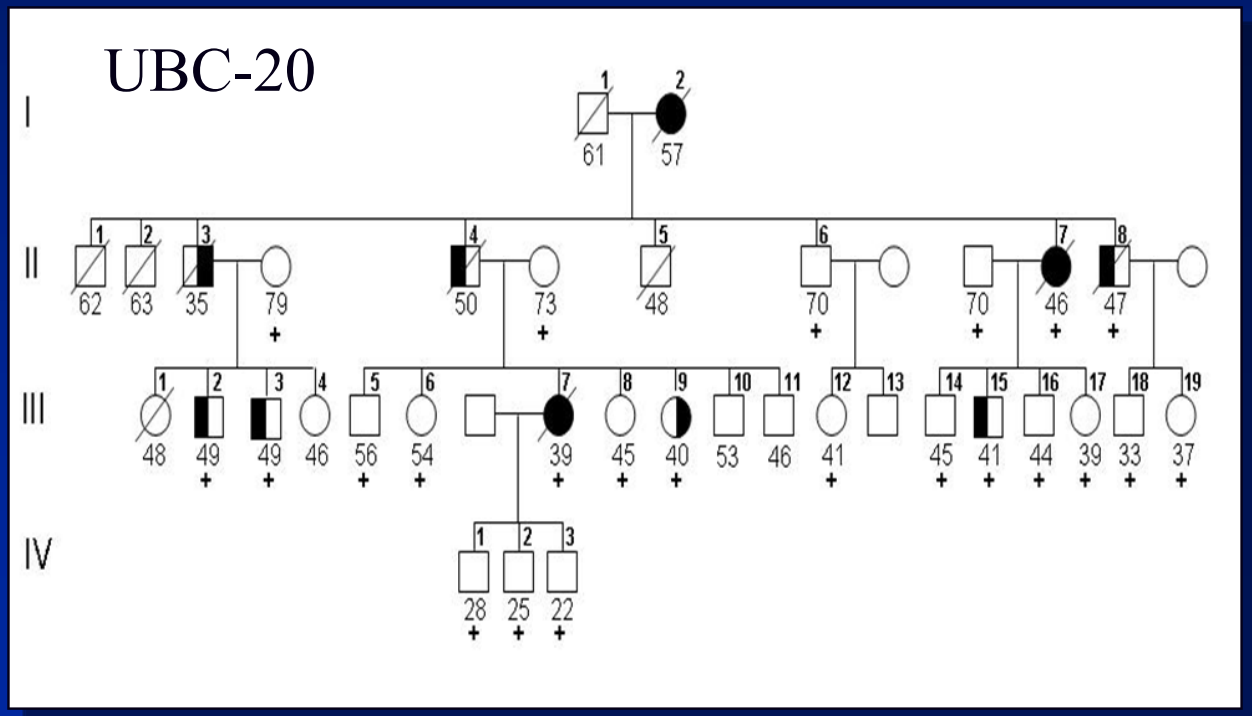
NiCole Finch,[1] Matt Baker,[1] Richard Crook,[1] Katie Swanson,[1] Karen Kuntz,[2] Rebecca Surtees,[1] Gina Bisceglio,[1] Anne Rovelet-Lecrux,[3] Bradley Boeve,[2] Ronald C. Petersen,[2] Dennis W. Dickson,[1] Steven G. Younkin,[1] Vincent Deramecourt,[4] Julia Crook,[1] Neill R. Graff-Radford[5] and Rosa Rademakers[1]

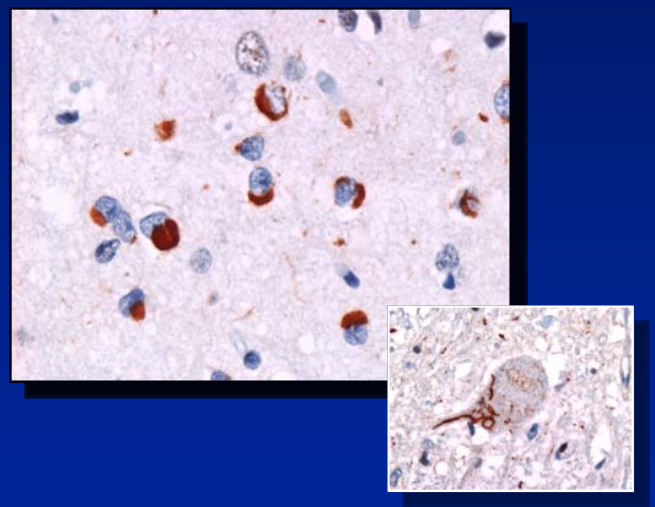




FTD/ALS linked to chromosome 9

- multiple families reported with combination of FTD and ALS showing genetic linkage to region on chromosome 9.

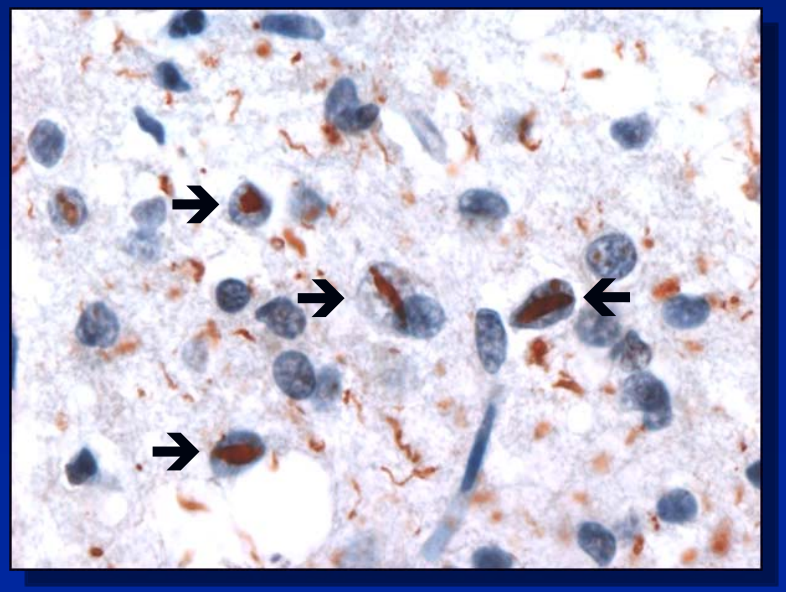




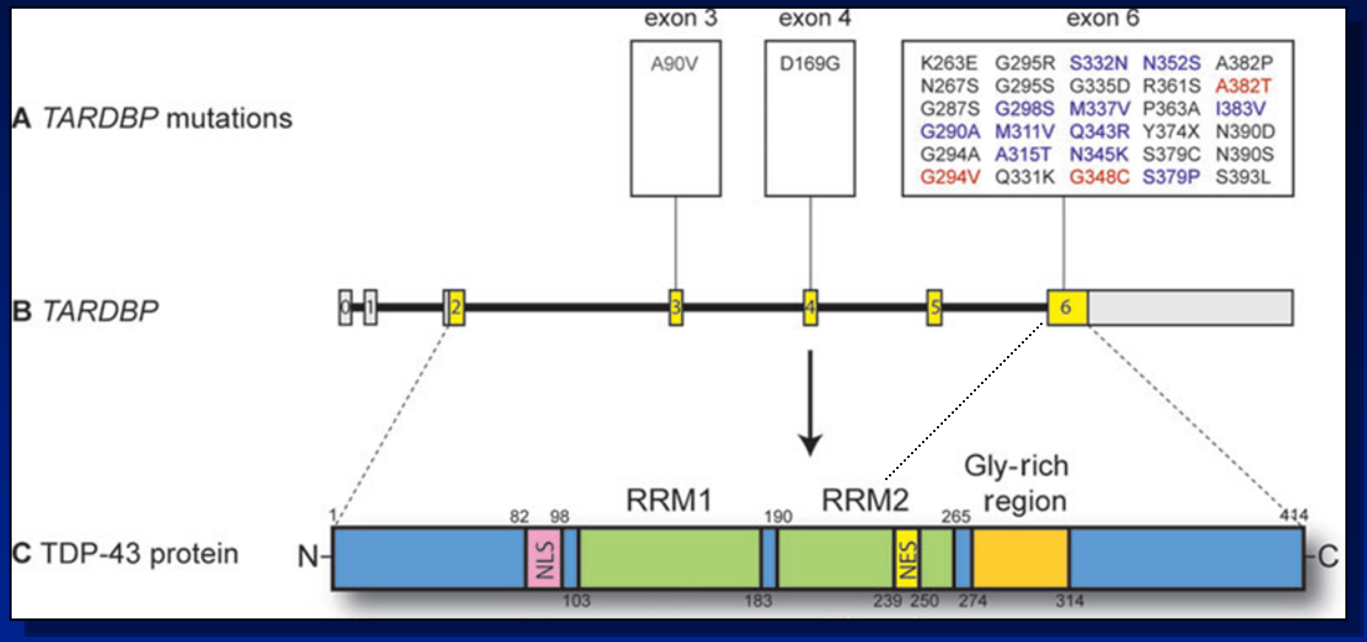
- FTLD-TDP type 3 and ALS.

Inclusion body myopathy with Paget's disease of bone and FTD

- rare autosomal dominant syndrome.
- myopathy (80%), Paget's disease of bone (50%), early-onset FTD (30%).
- mutations in the gene for valosin-containing protein (*VCP*).
- FTLD-TDP type 4.



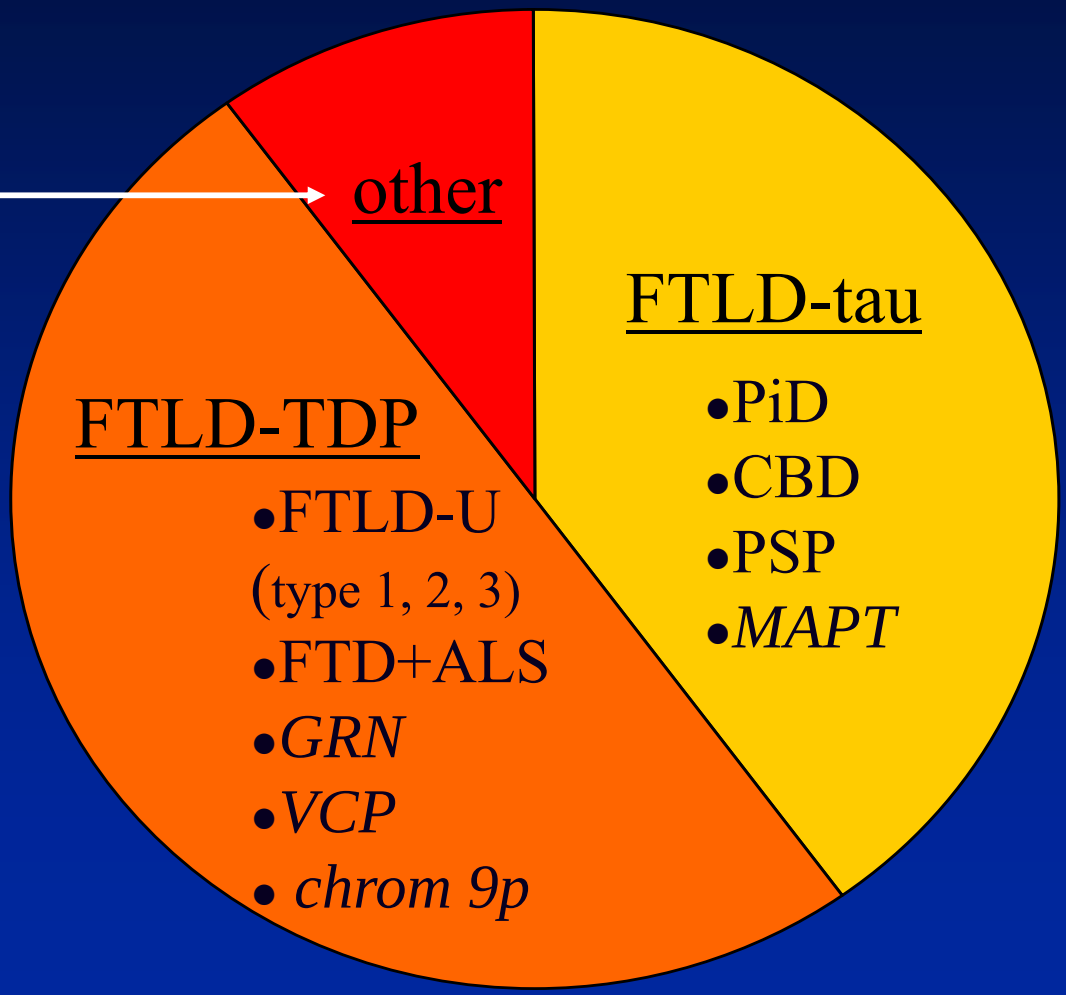
TARDBP mutations in ALS



- 38 missense mutations in 78 families.
- ~3% FALS and ~1.5% SALS.
- clinically and pathologically typical ALS.
- rare mutations in familial and sporadic FTD +/- ALS.

Neuropathology of FTD

- aFTLD-U
- NIFID
- BIBD
- DLDH
- *CHMP2B*

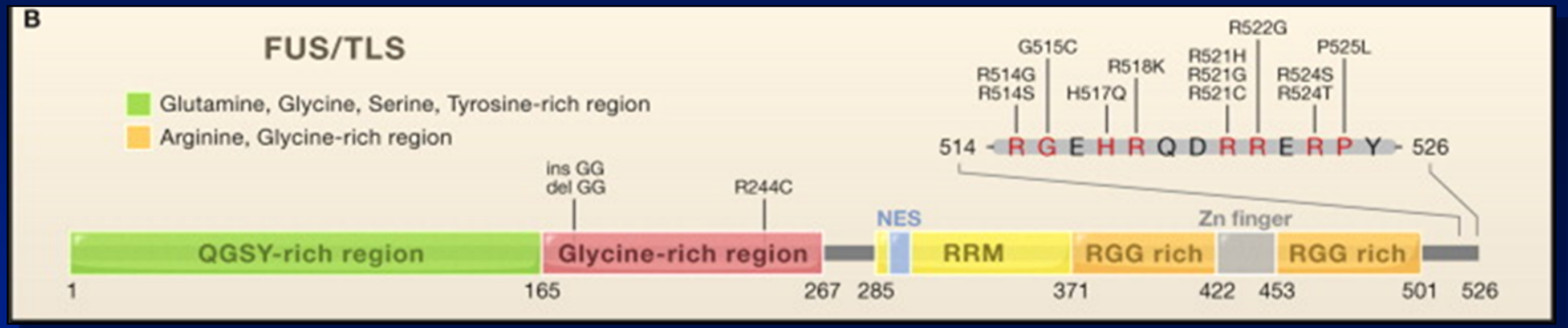


Mutations in the *FUS/TLS* Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis

T. J. Kwiatkowski Jr.,[1*] D. A. Bosco,[1,2] A. L. LeClerc,[1,2] E. Tamrazian,[1] C. R. Vanderburg,[3] C. Russ,[1,4] A. Davis,[1] J. Gilchrist,[5] E. J. Kasarskis,[6] T. Munsat,[7†] P. Valdmanis,[8] G. A. Rouleau,[8] B. A. Hosler,[1] P. Cortelli,[9] P. J. de Jong,[10] Y. Yoshinaga,[10] J. L. Haines,[11] M. A. Pericak-Vance,[12] J. Yan,[13] N. Ticozzi,[1,2,14] T. Siddique,[13] D. McKenna-Yasek,[1] P. C. Sapp,[1,15] H. R. Horvitz,[15] J. E. Landers,[1,2] R. H. Brown Jr.[1,2*]

Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6

Caroline Vance,[1*] Boris Rogelj,[1*] Tibor Hortobágyi,[1*] Kurt J. De Vos,[2*] Agnes Lumi Nishimura,[1] Jemeen Sreedharan,[1] Xun Hu,[1] Bradley Smith,[1] Deborah Ruddy,[1] Paul Wright,[1] Jeban Ganesalingam,[1] Kelly L. Williams,[3] Vineeta Tripathi,[1] Safa Al-Saraj,[1] Ammar Al-Chalabi,[1] P. Nigel Leigh,[1] Ian P. Blair,[3,5] Garth Nicholson,[3,4,5] Jackie de Belleroche,[6] Jean-Marc Gallo,[1] Christopher C. Miller,[1,2] Christopher E. Shaw[1†]



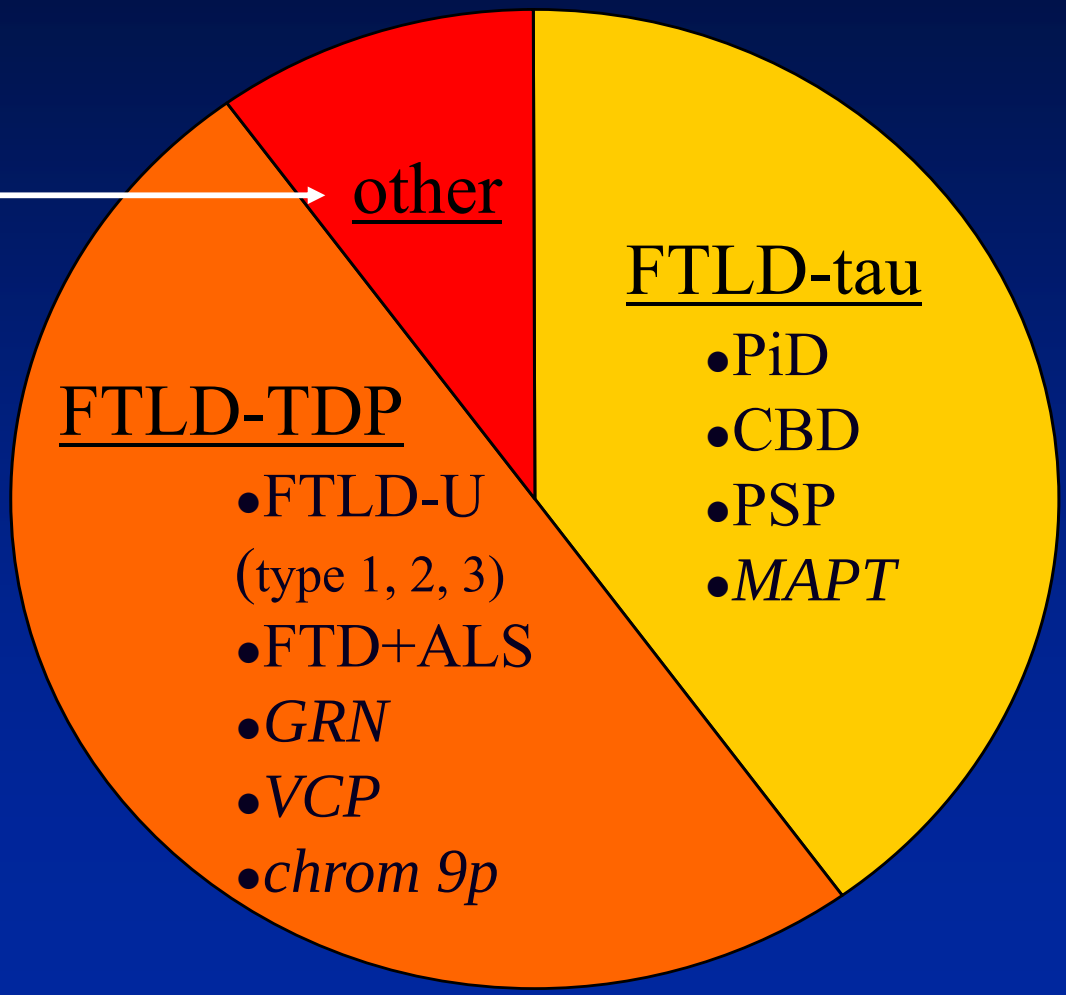
- *fused in sarcoma / translocated in liposarcoma*.
- RNA/DNA binding protein with similar function to TDP-43.
- mutations → ~4% FALS and <1% SALS.
- pathology = TDP-43-negative, FUS-positive inclusions.

Science, Feb. 27, 2009

Neuropathology of FTD

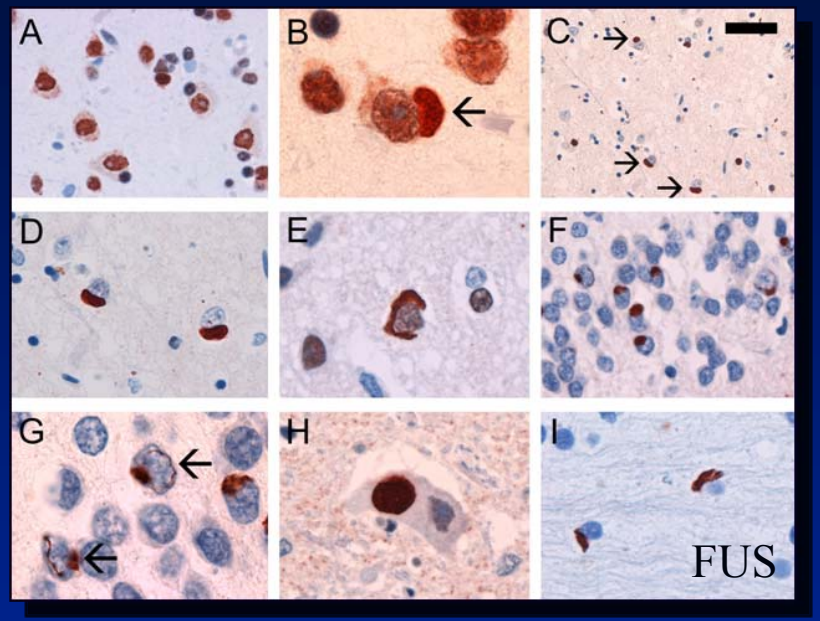
- aFTLD-U
- NIFID
- BIBD
- DLDH
- *CHMP2B*

FUS?

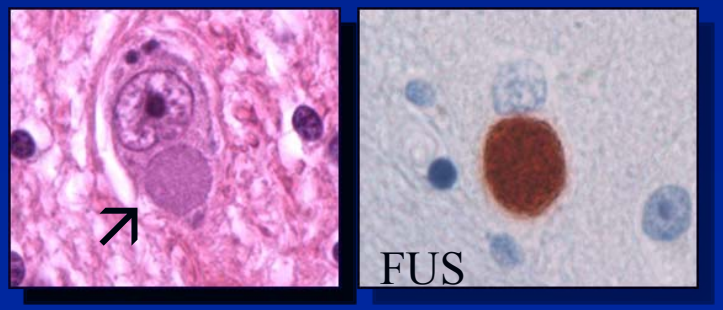


FTLD-FUS

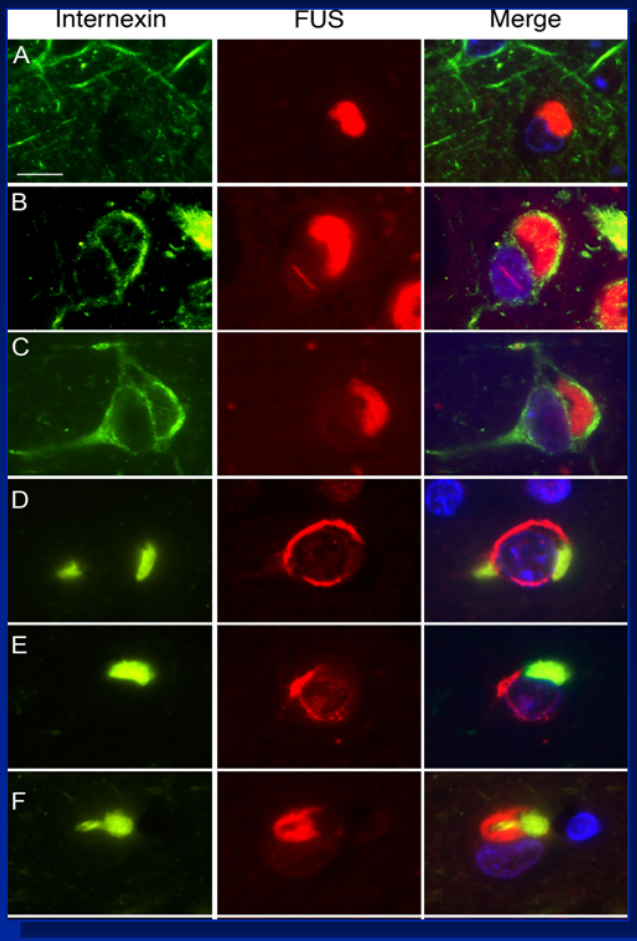
"Atypical" FTLD-U



Basophilic inclusion body disease



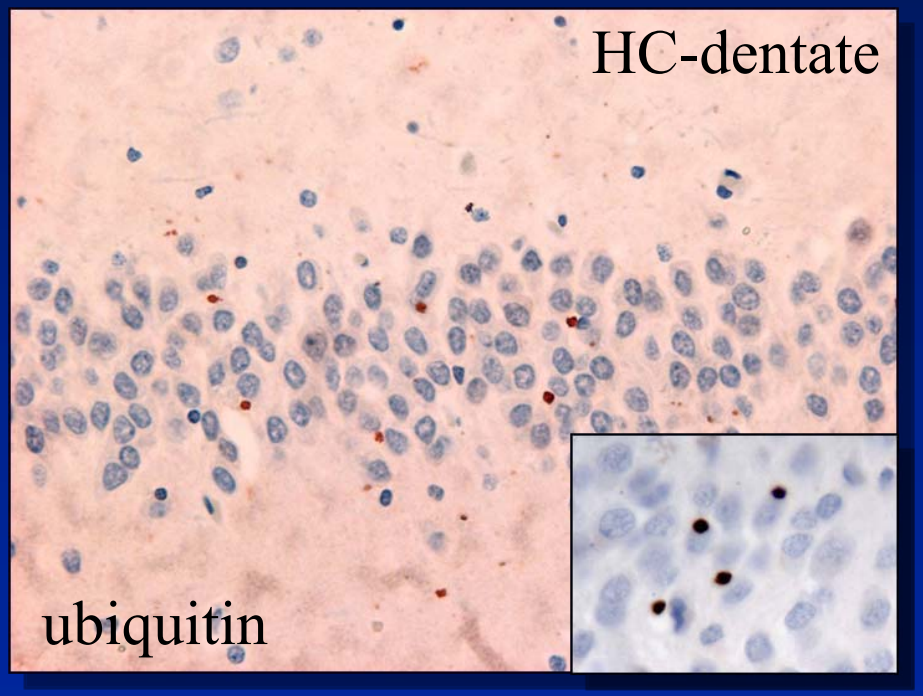
Neuronal intermediate filament inclusion disease

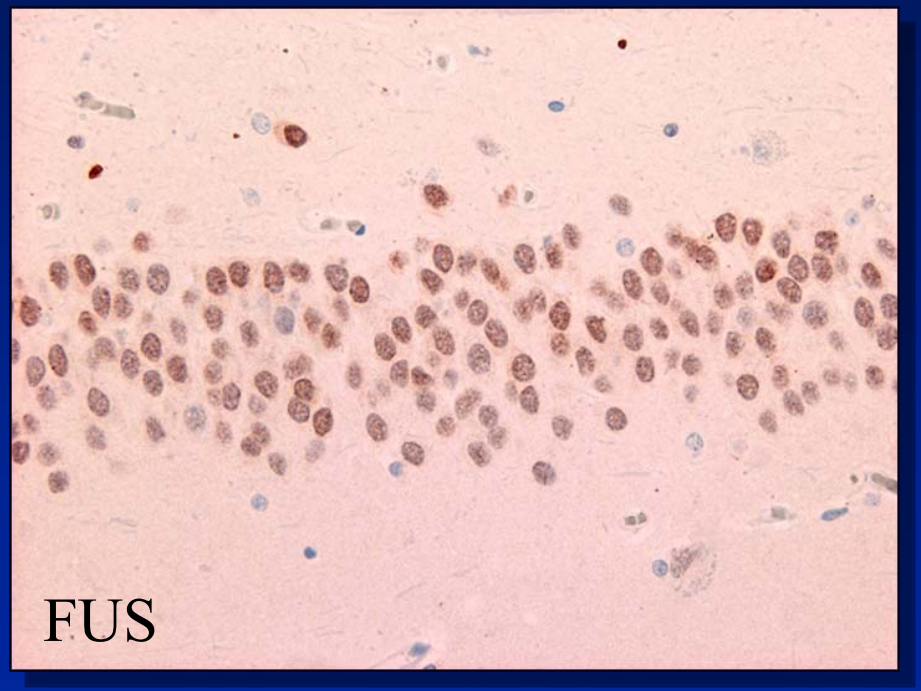


- most tau/TDP-negative FTLD is FUS+.

FTD linked to chromosome 3

- single Danish family with FTD caused by mutation in *CHMP2B* gene.





- ubiquitin+ inclusions do not label for tau, TDP-43 or FUS.

Neuropathology of FTD