Neuropathology

Neurodegenerative disorders

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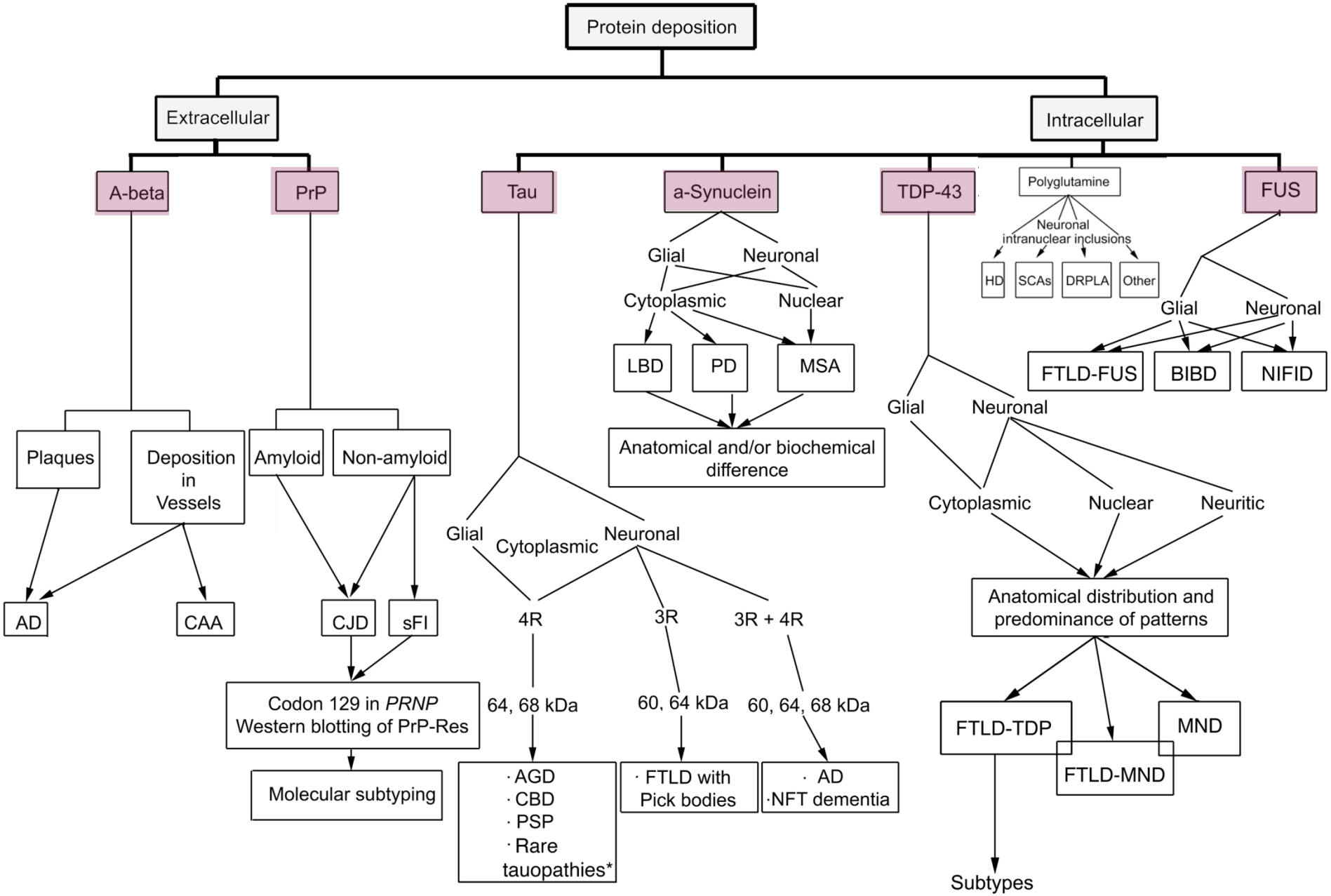
Primary neurodegenerative diseases

- **Degeneration of subsets of neurons that typically are related by function (selective neuronal vulnerability)**
- **Accumulation of abnormal proteins – characteristic of a disease – is often seen**
- **Symptoms depend on the affected brain regions**
  - **Dementia/cognitive decline (cortical neurons, hippocampus)**
  - **Movement disorders: hypo- or hyperkinetic (neurons of the basal ganglia)**
  - **Ataxia (cerebellum)**
  - **Weakness (motoneurons)**
  - **Mixed**

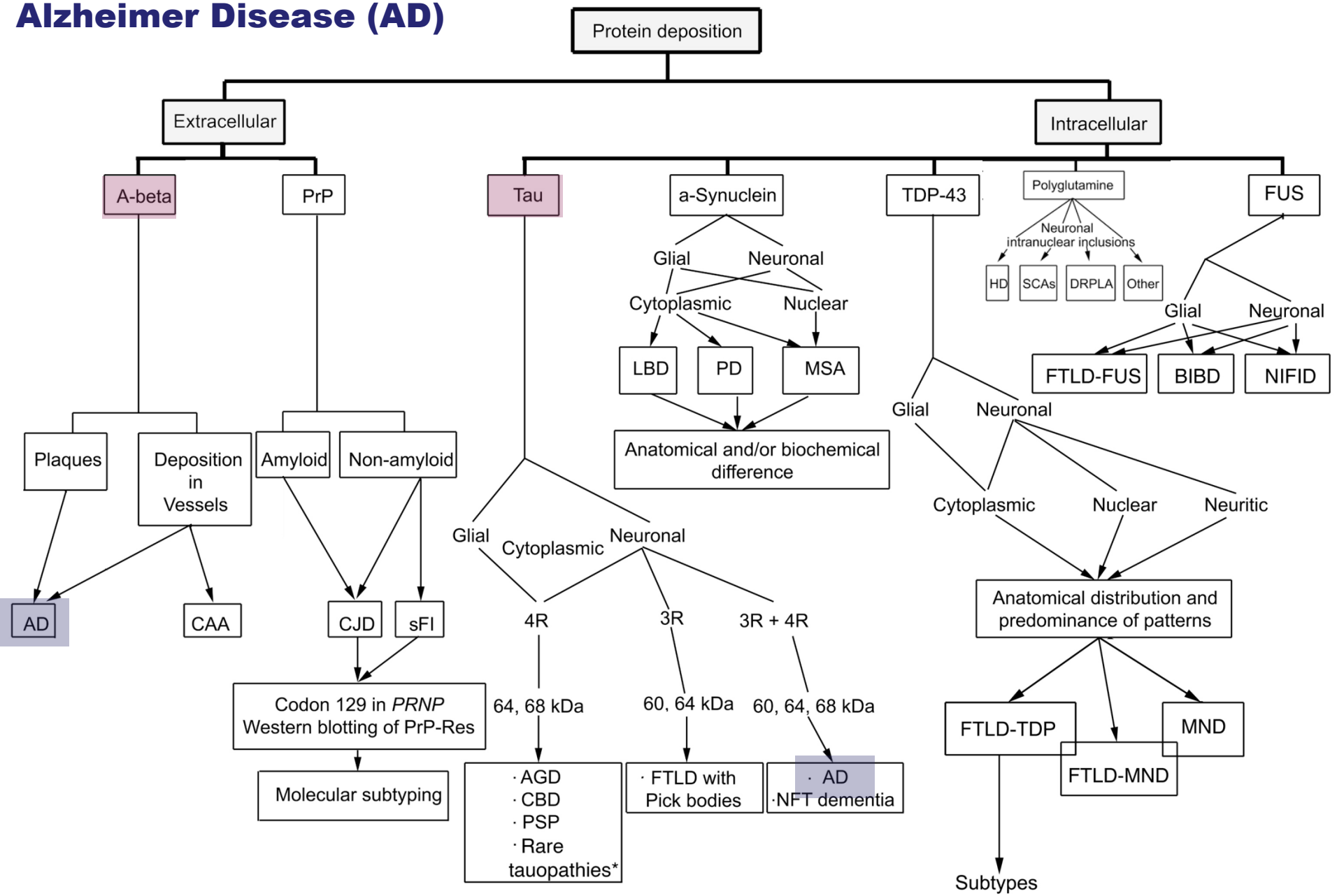
Primary neurodegenerative diseases – abnormal proteins

- **Normal cellular protein develops an abnormal conformation**
- **Imbalance in protein metabolism**
- **The (abnormal) protein aggregates and accumulates intra- or extracellular**
- **E.g.: Tau, alpha-synuclein, beta-amyloid, TDP-43, FUS, prion**



Kovács GG. et al. 2010 Acta Neuropath.

Alzheimer Disease (AD)



Kovács GG. et al. 2010 Acta Neuropath.

Alzheimer Disease (AD)

- **Prevalence**

  60-64 ys: 1%

  85 ys: 50%

- **Incidence rate increases with age**

  70-80 ys: 1-2 case/100 persons/year

  after 80 ys: 2-8 case/100 persons/year

- **Disease duration is ~7 ys (2-18)**

Alzheimer Disease (AD)

- **Initially: memory and cognitive problems**

  (e.g.: they get lost, unable to cope with new situations, cannot dress up etc.)

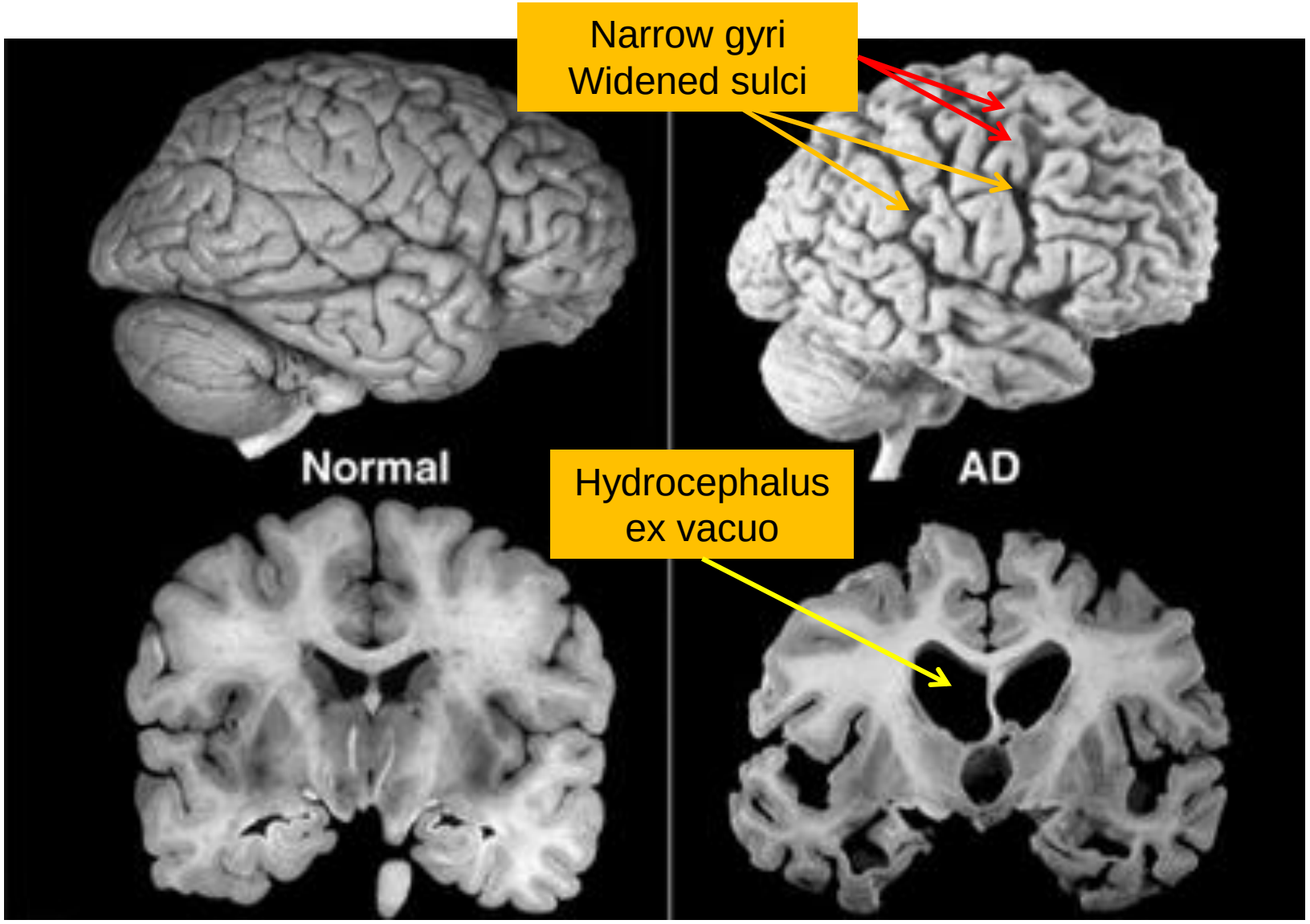
- **Later: psychiatric and behavioral problems, incontinency, etc.**
- **Terminally: severe cognitive decline, unable to move, mutism**

Alzheimer Disease (AD)

- **Sporadic (90-95%) – „late onset”**
  - **Multiple genetic and environmental factors**

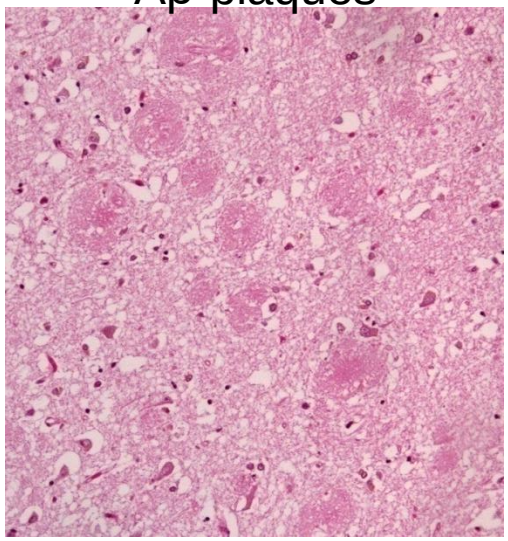
- **Familial (5-10%) – „early onset”**
  - **AuD inheritance**
  - **Mutations in Presenilin-1 & -2 (coding components of γ-secretase), and amyloid precursor protein**
  - **<60 ys**

AD macro-morphology: Atrophy

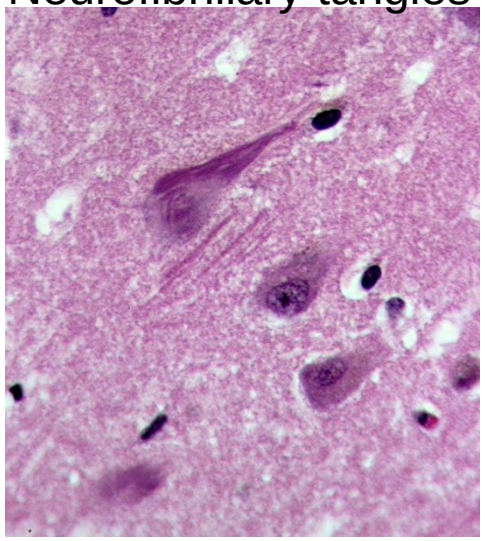


AD micro-morphology: Amyloid plaques & Neurofibrillary tangles

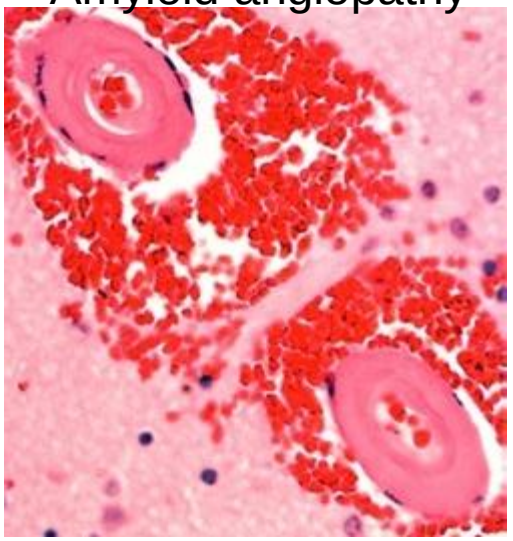
Aβ-plaques



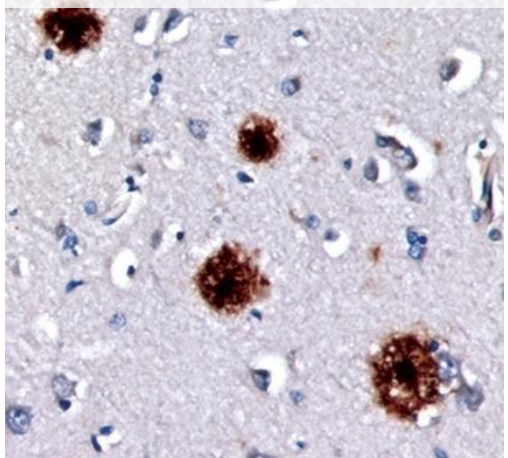
Neurofibrillary tangles



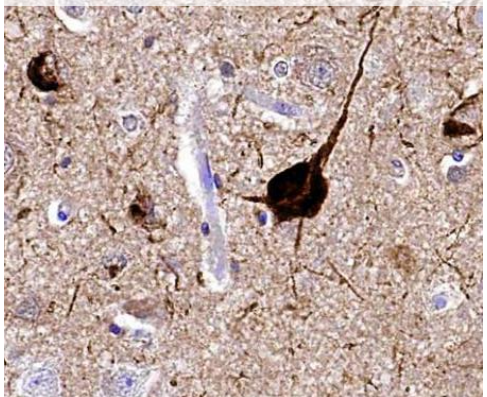
Amyloid angiopathy



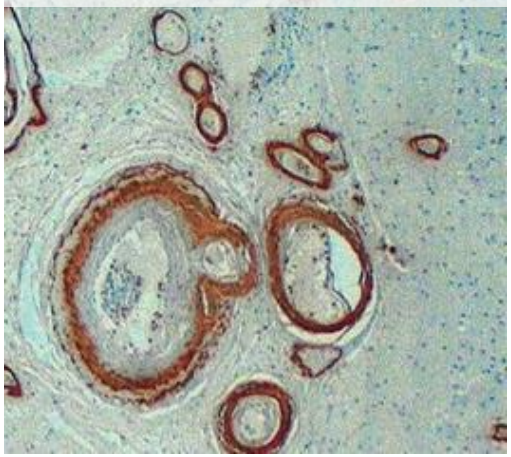
β-amyloid



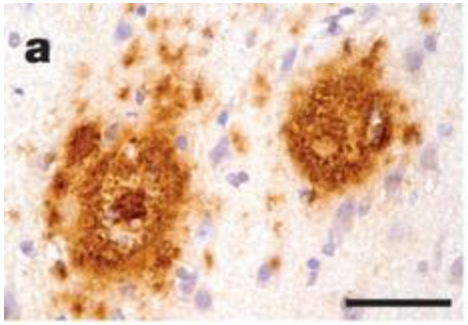
Hyperphosphorilated Tau

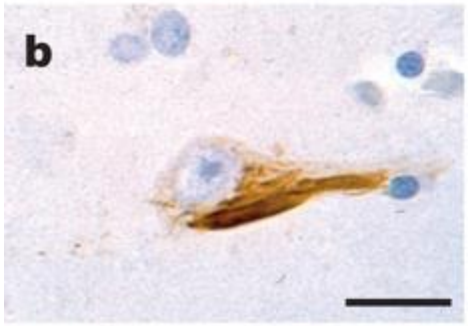


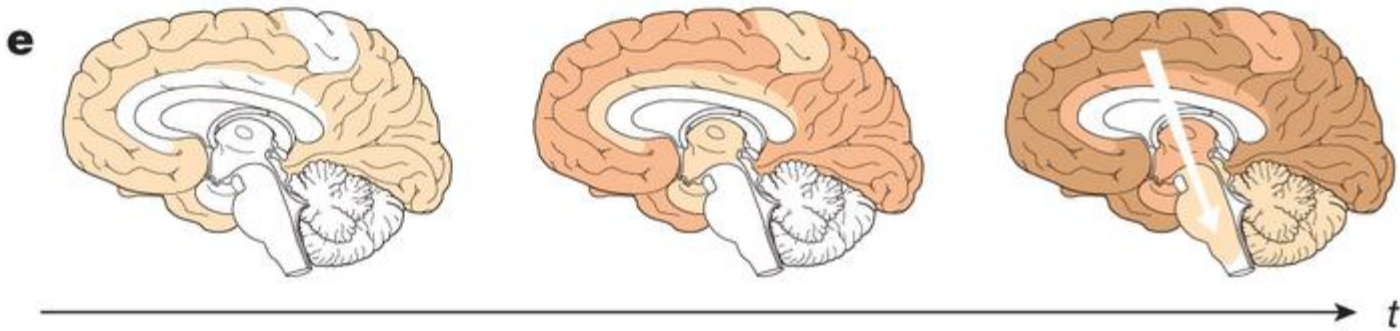
β-amyloid

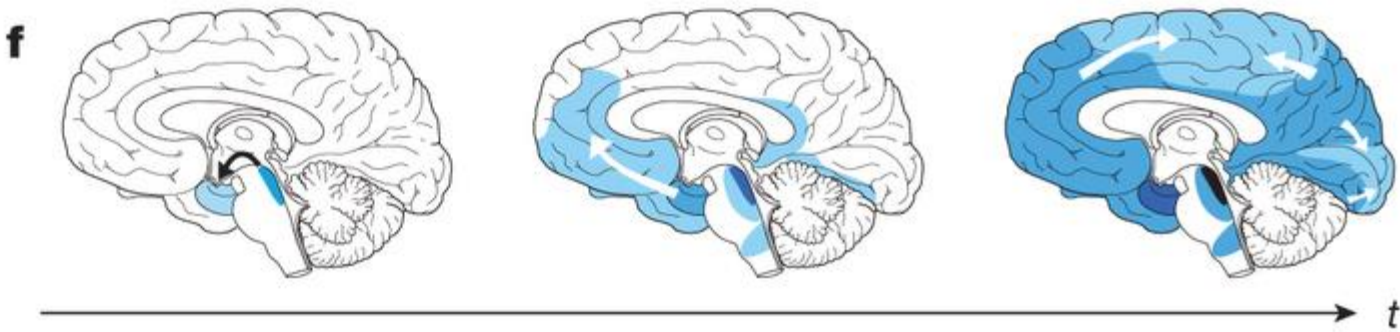


Amyloid-beta plaques & neurofibrillary tangles accumulate in the brain in a characteristic way with disease progression



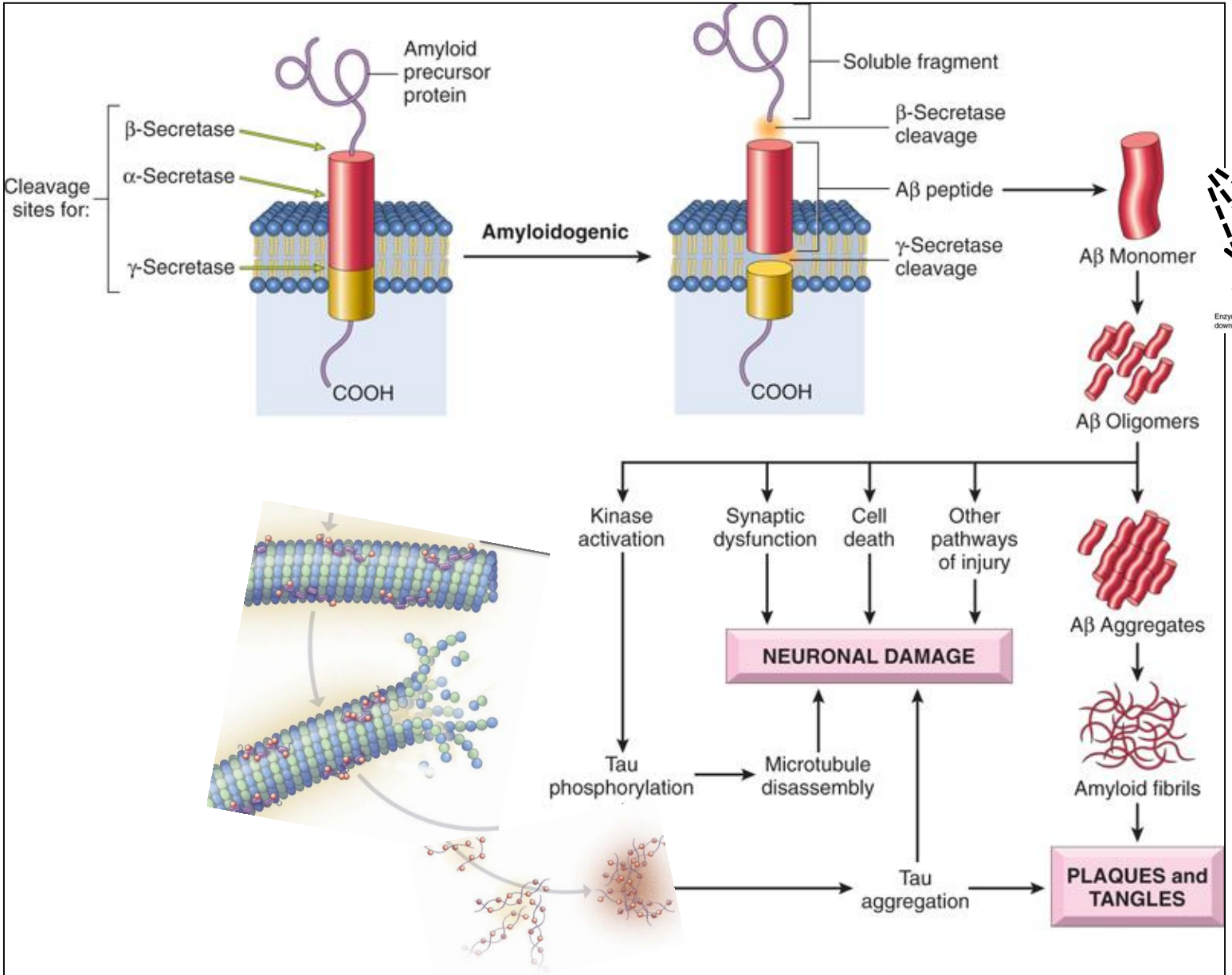




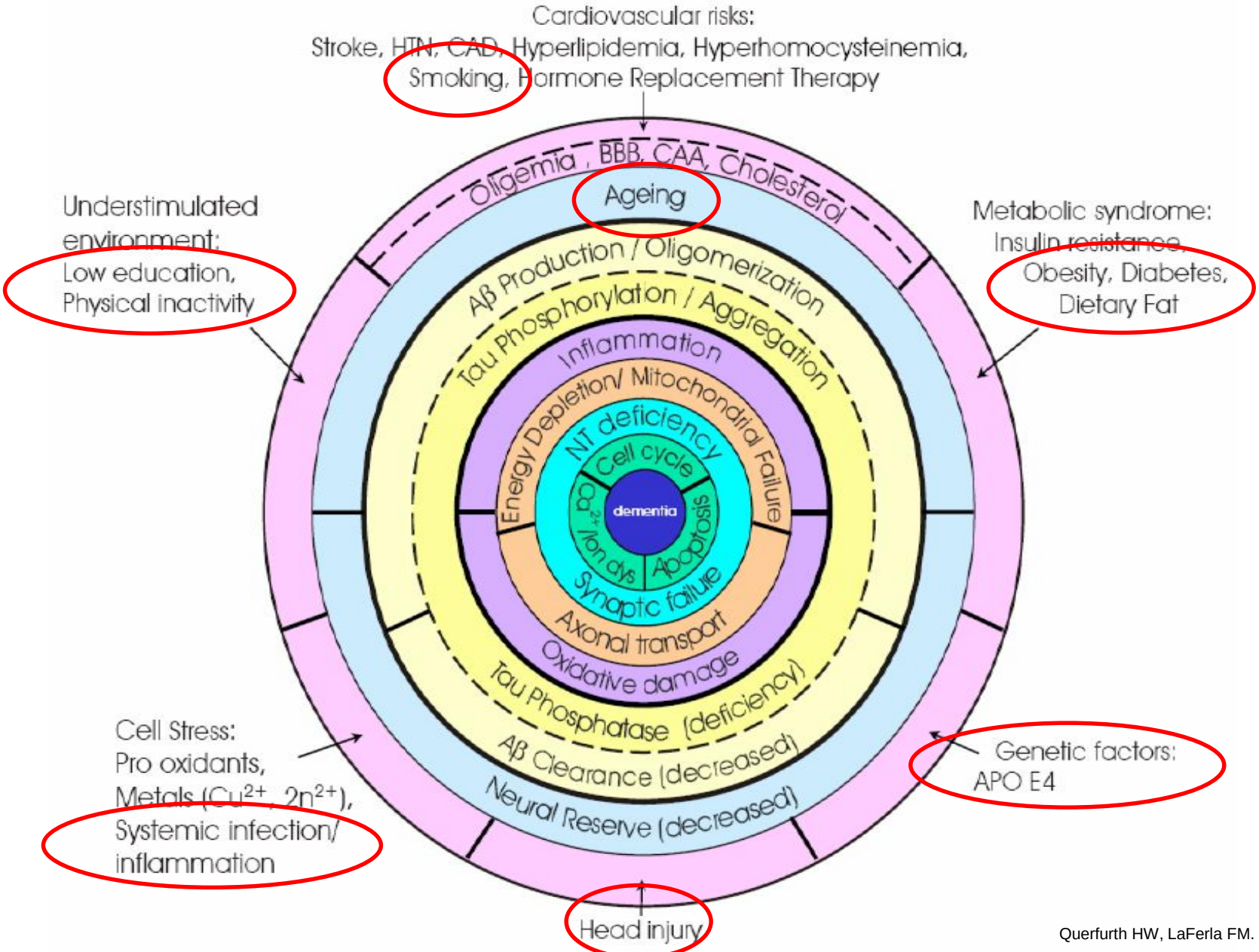


Jucker M, Walker LC. Nature, 2013

Aβ-peptide is produced by cleavage of APP. Aβ-oligomers are neurotoxic.



Risk factors and molecular mechanisms in the pathogenesis of Alzheimer disease



Querfurth HW, LaFerla FM. NEJM, 2010

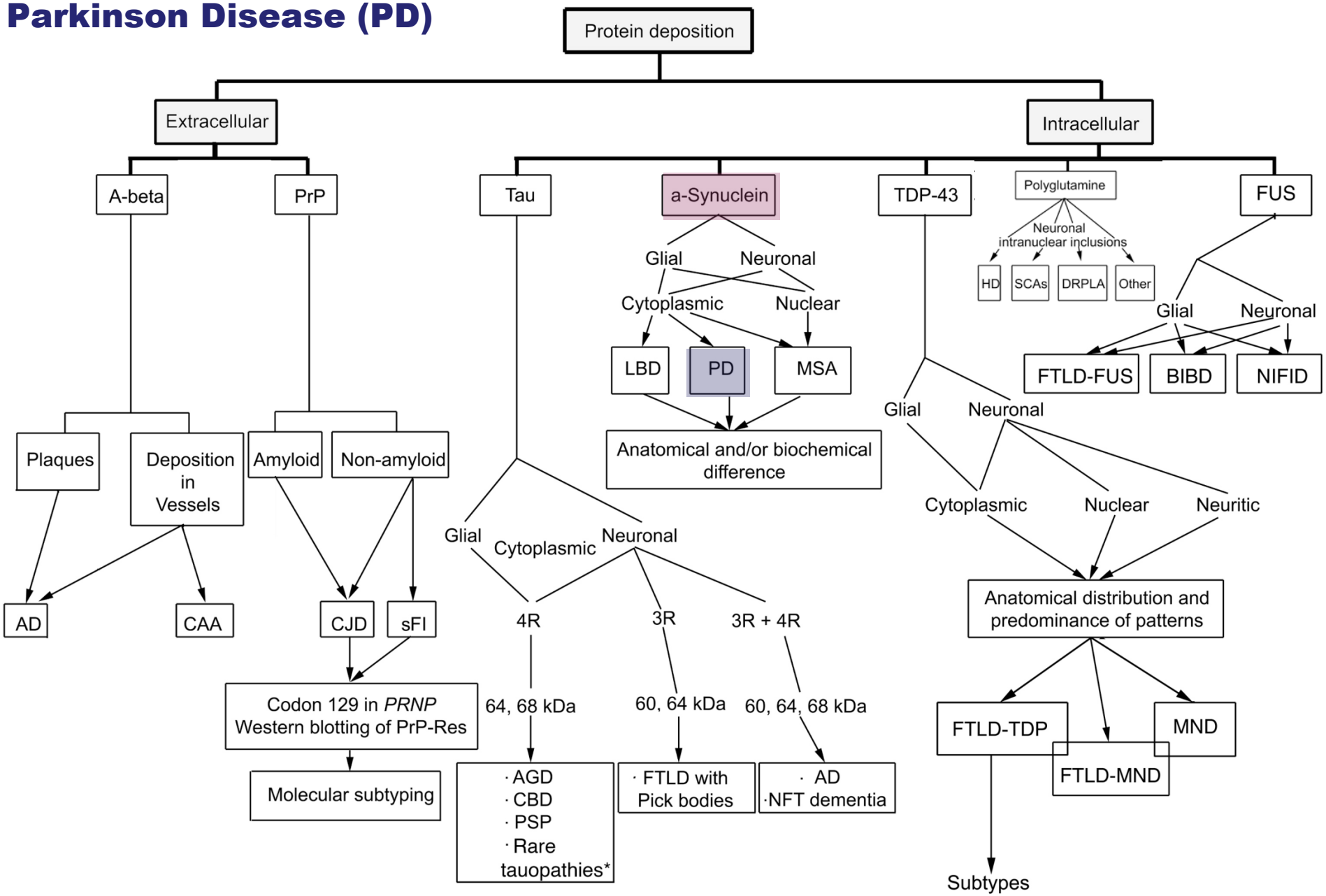
Genetic risk factors in Alzheimer disease

Gene name (symbol)	Chromosomal location	Function of encoded protein
Apolipoprotein E (*APOE*)	19q13.2	Transportation of lipoproteins, fat-soluble vitamins, and cholesterol
Myc box-dependent-interacting protein 1 (*BIN1*)	2q14.3	Tumor suppressor
ATP binding cassette transporter 7 (*ABCA7*)	19p13.3	The expression pattern suggests a role for lipid homeostasis and differentiation of immune cells.
Membrane-spanning 4-domains, subfamily A (*MS4A*)	11q12.2	Possibly involved in signal transduction or immunological functions
Ephrin type-A receptor 1 (*EPHA1*)	7q34	Member of the EPH receptor-tyrosine kinase family, implicated in mediating developmental events of the nervous system
CD33 antigen (*CD33*)	19q13.3	Adhesion molecule of myelomonocytic-derived cells
CD2 associated protein (*CD2AP*)	6p12.3	A scaffolding molecule that regulates the actin cytoskeleton and vesicle formation
Sortilin-related receptor 1 (*SORL1*)	11q24.1	Receptor for ApoE, assists with intracellular trafficking and processing of APP

APOE4 allele – increases Aβ aggregation and decreases its clearance
1 allele – 4x risk
2 alleles – 19x risk
Not enough to develop AD

Barber RC. Scientifica, 2012

Parkinson Disease (PD)



Kovács GG. et al. 2010 Acta Neuropath.

Parkinson Disease (PD)

- **Common (10-20 new case/100 000/y)**
- **After 60 ys (40-70 ys)**
- **Loss of dopaminergic neurons**
- **Specific movement symptoms:**

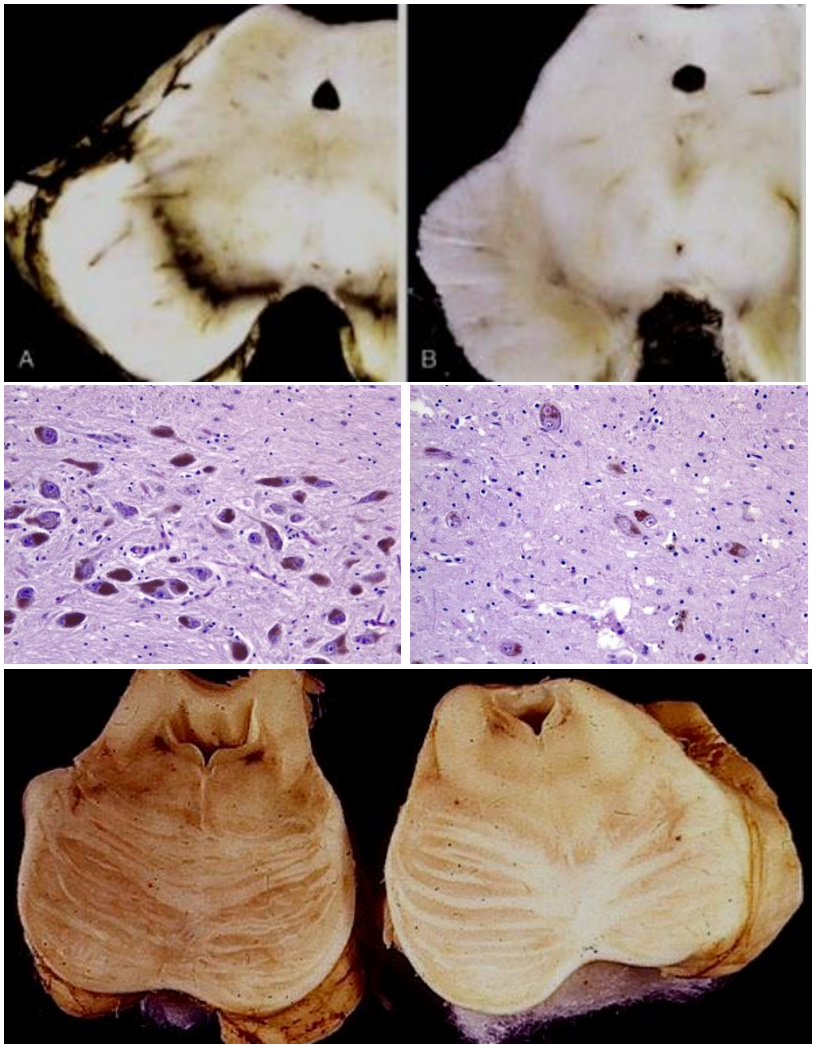
  tremor, rigidity, bradykinesia, instability
- **+/- Dementia**
- **Autonomic dysfunction and behavioral disorders often present in advance motor problems**

Parkinson Disease (PD)

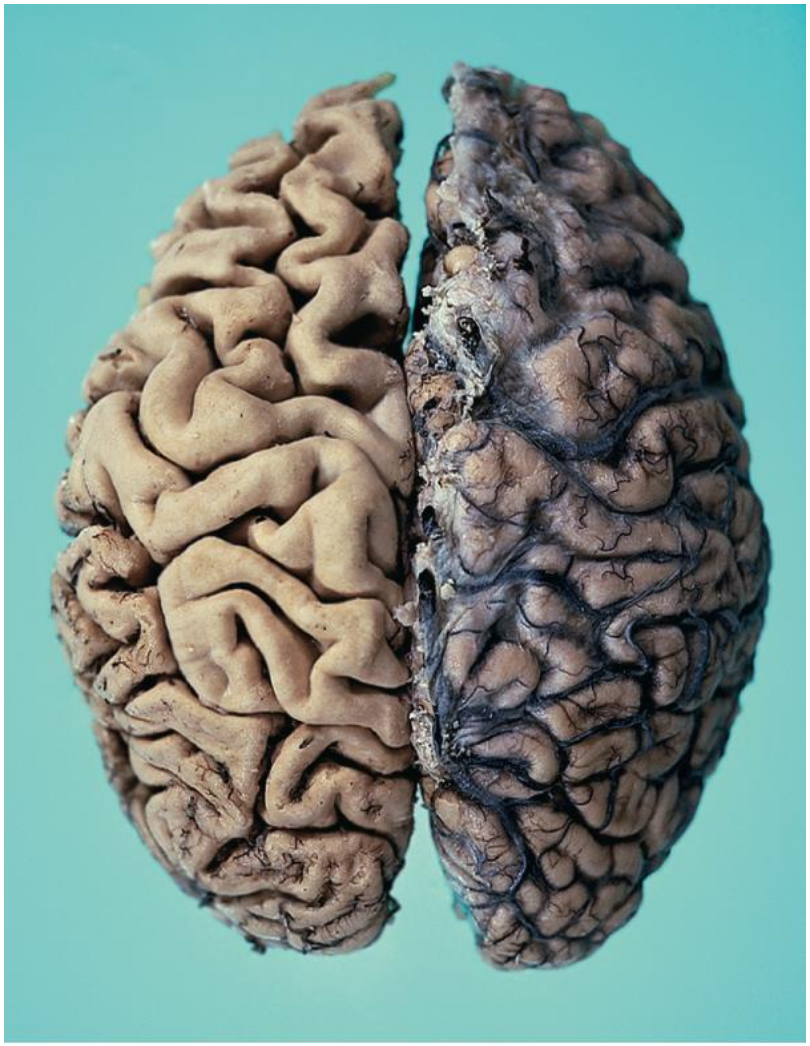
- **Sporadic**
  - **Multiple genetic and environmental factors**
- **Familial**
  - **AuDom inheritance: α-synuclein mutations/duplications**
  - **AuRec inheritance: Parkin, UCHL-1, LRRK2, PARK7, PINK1, etc. mutations**

PD macro-morphology: SN & LC are pale (depigmented)

Normal **PD**

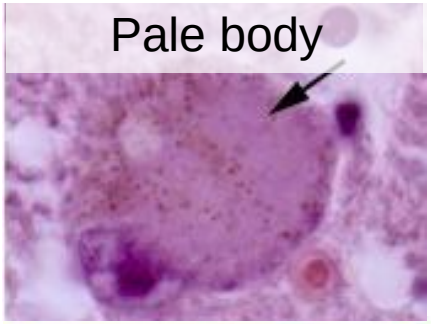


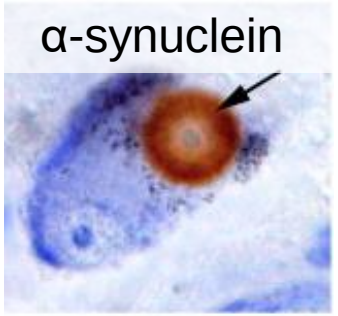
+/- Diffuse cortical atrophy

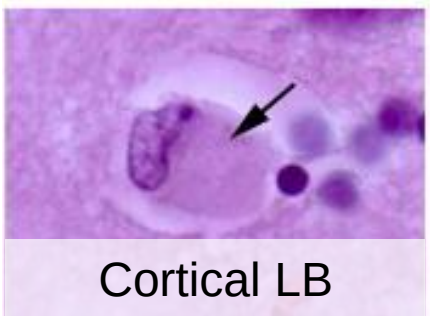


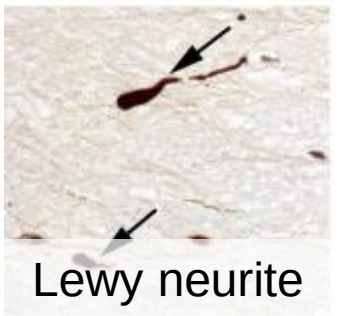
PD micro-morphology: Neuronal loss, Lewy bodies

- **Dop. neurons of the substantia nigra & locus coeroleus are lost**
- **Lewy bodies and Lewy neurites:**
  - **SN, LC, pons, medulla oblong., cortical & subcortical areas**
  - **contain α-synuclein**
- **Cortical involvement – dementia**
- **Pale bodies**

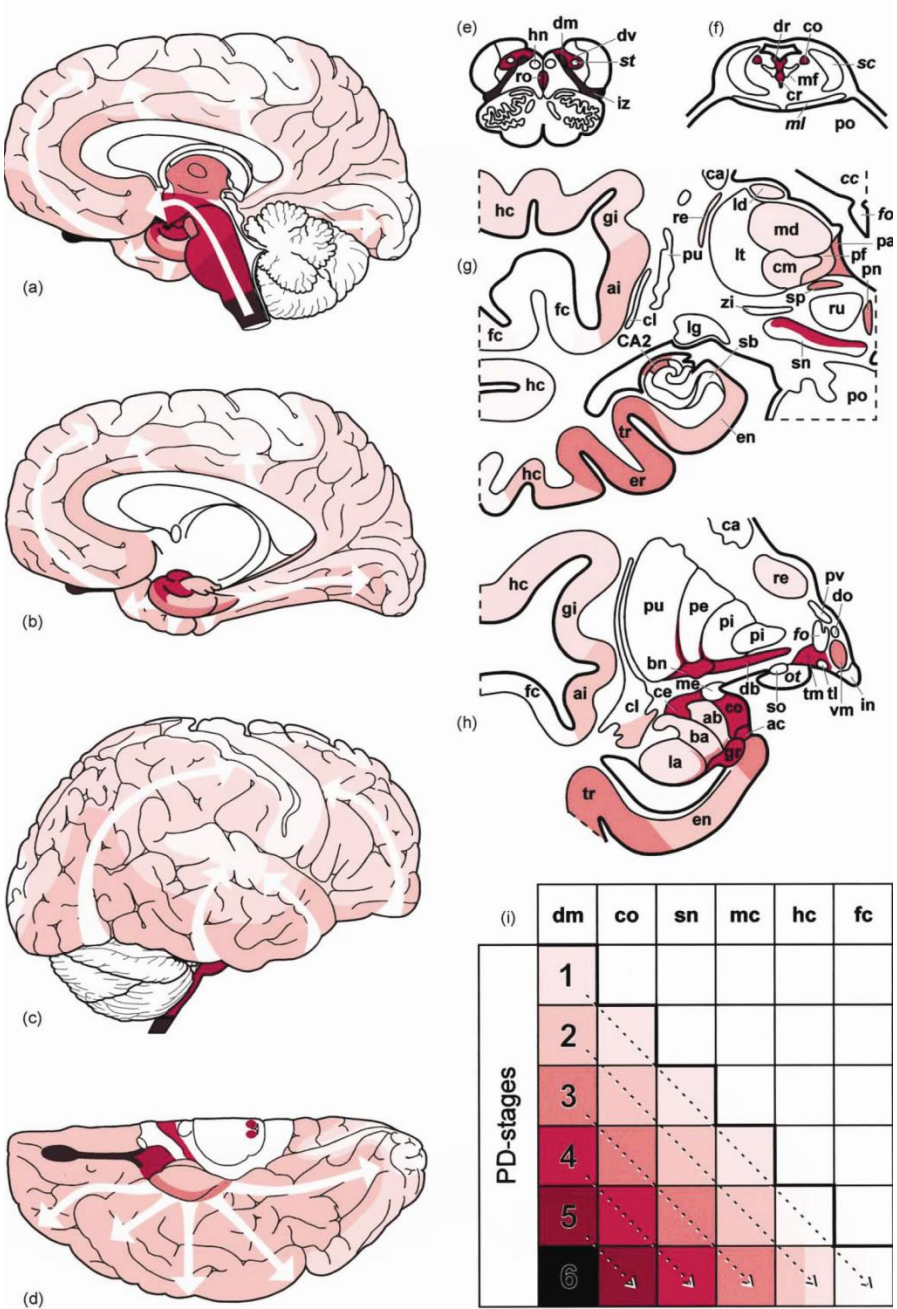






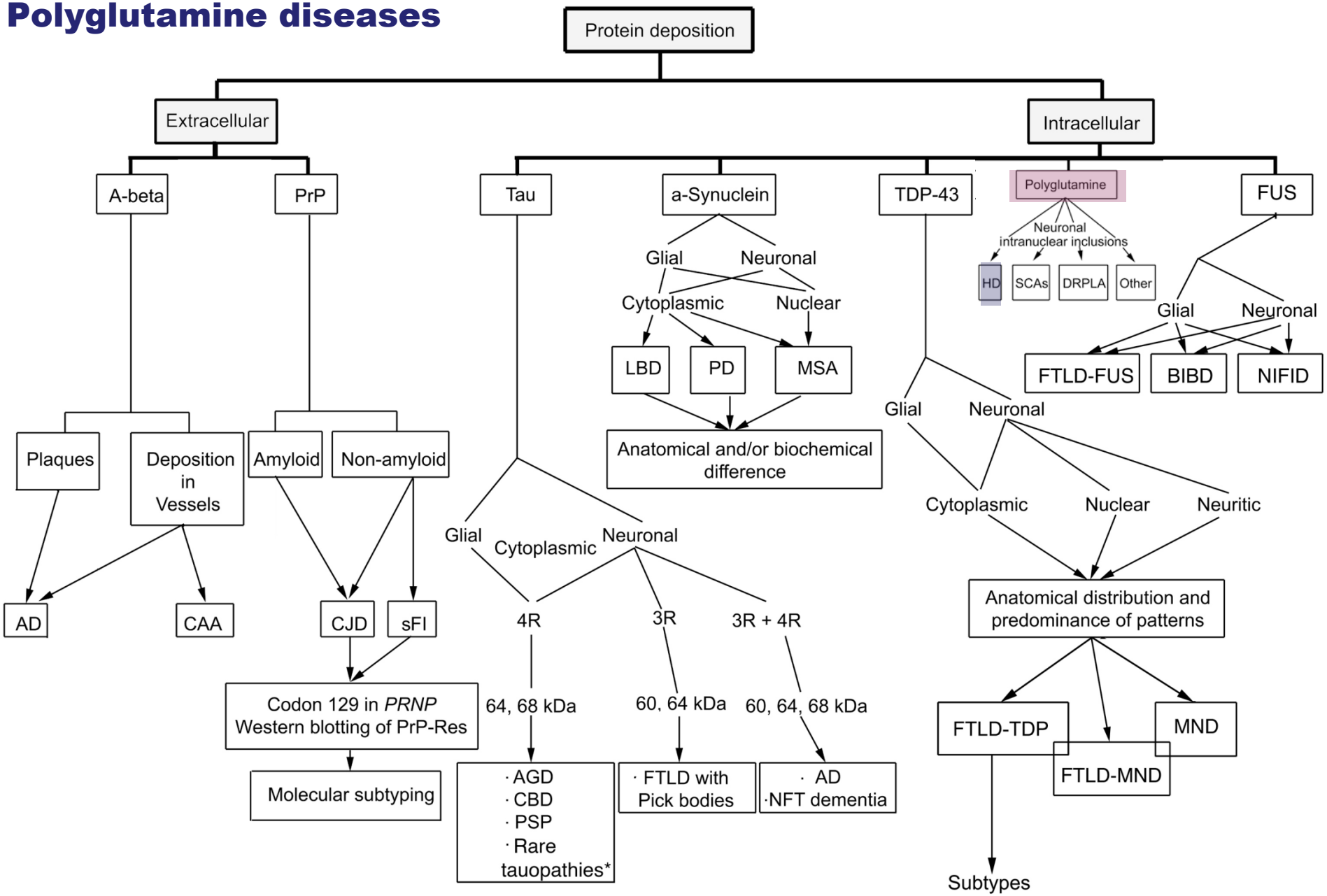


Progression of PD pathology



Braak H et al. Neurobiol. Aging. 2003

Polyglutamine diseases



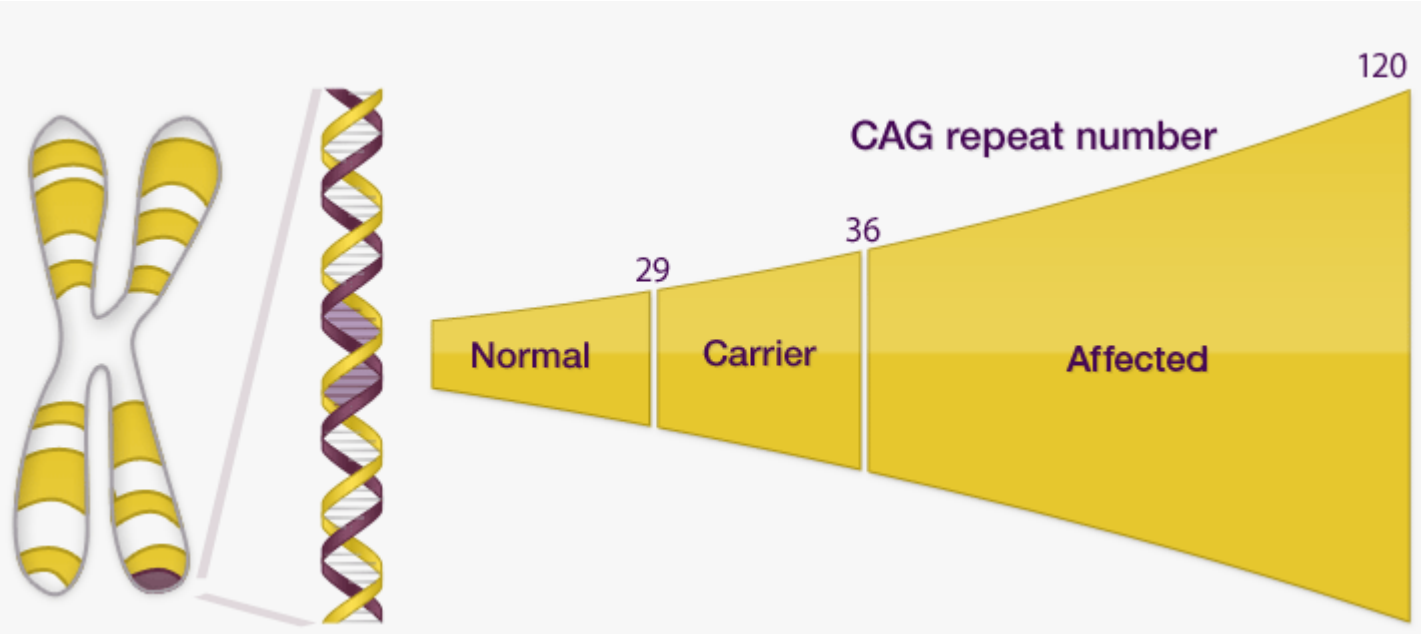
Kovács GG. et al. 2010 Acta Neuropath.

Huntington disease (HD)

- **Autosomal dominant inheritance**
- **CAG trinucleotid repeat disease**
- **Specific movement symptoms**
  - **Involuntary jerky/writhing/choreiform movements**
  - **Ataxia**
  - **Hyperkinesis**
- **Behavioral and affective disorders (increased risk for suicide), dementia**
- **Disease duration: 15 ys**

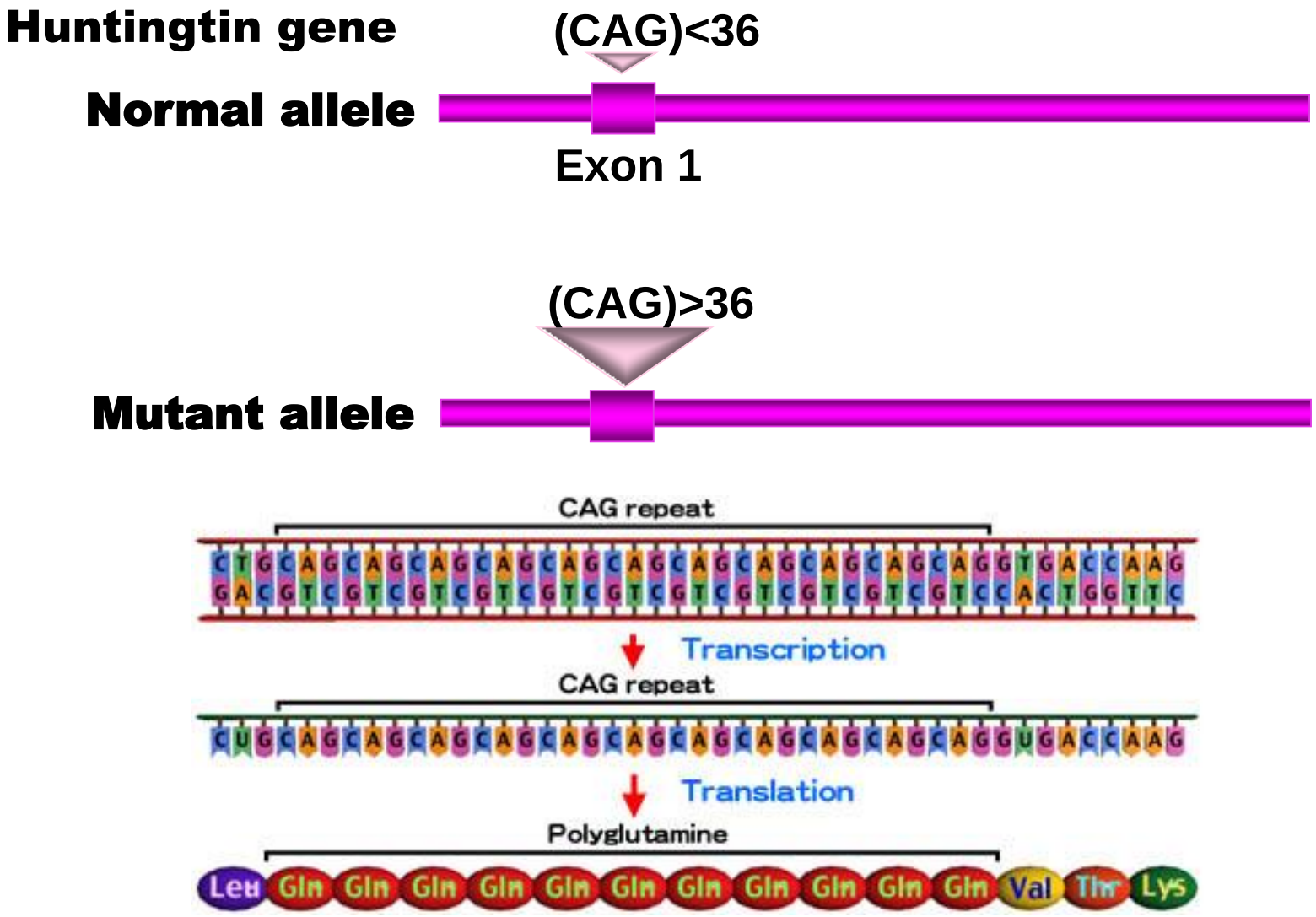
Huntington disease (HD)

4p16.3 – Huntingtin gene

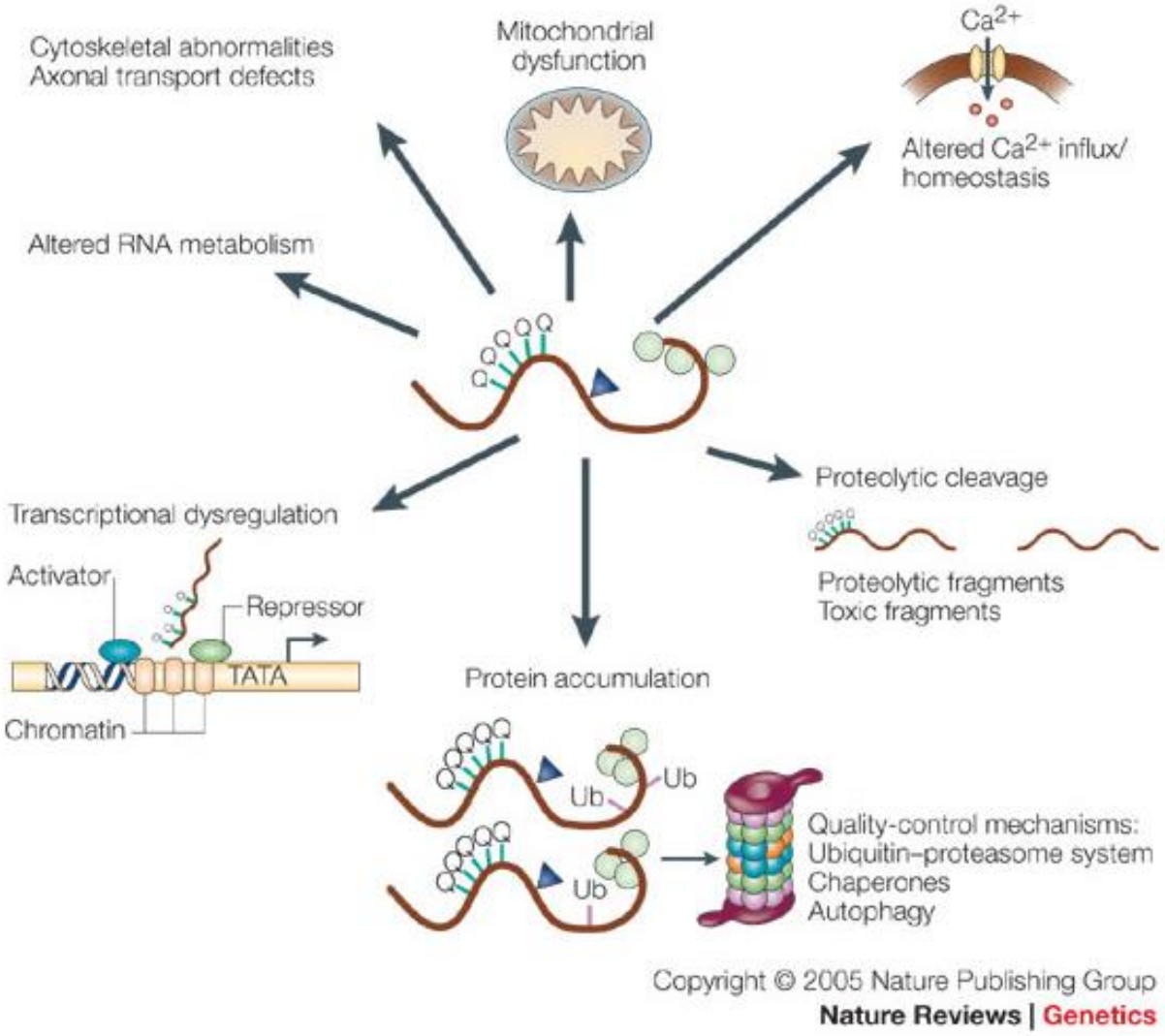


With increasing number of repeats, the disease starts at earlier ages (disease duration remains the same)

Expanded polyglutamine (polyQ) chain gains toxic function



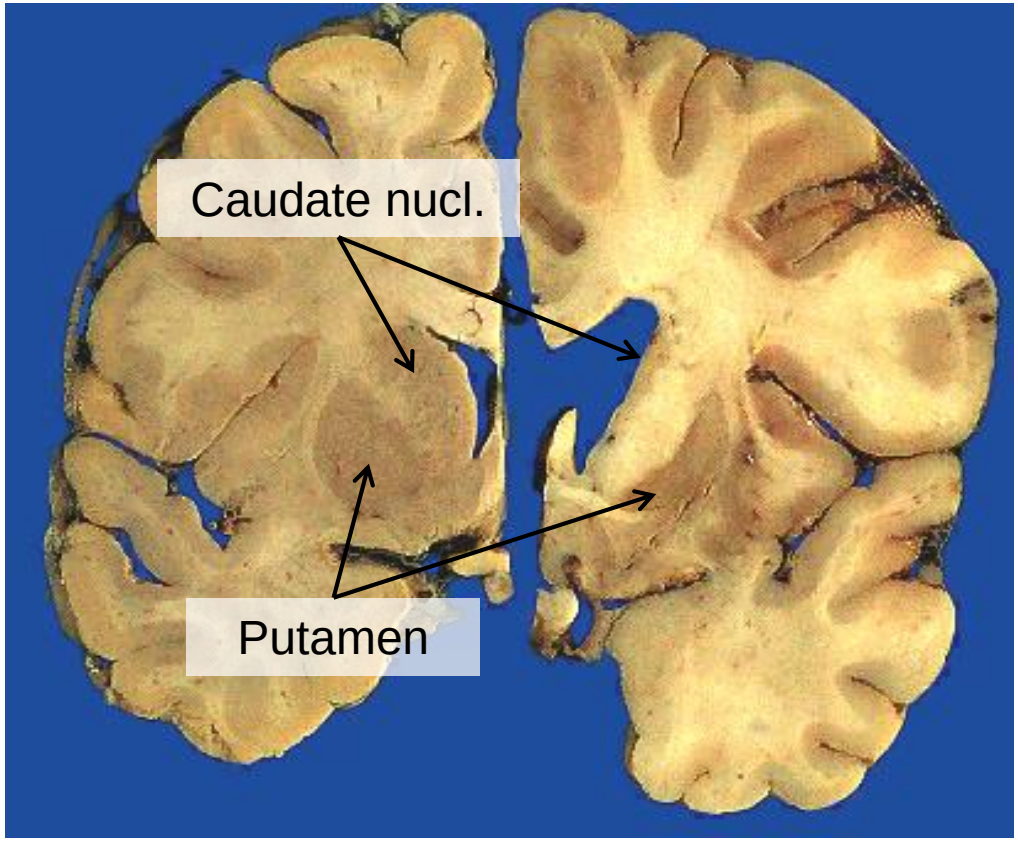
HD – toxic functions of mutant huntingtin protein

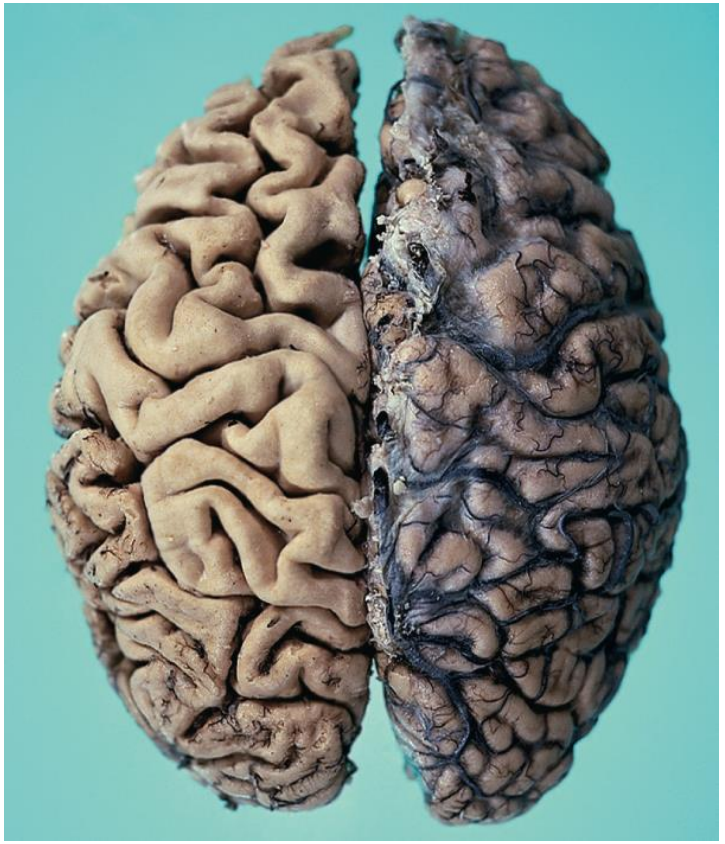


Nature Reviews | Genetics

HD macro-morphology: caudate nucl. & putamen atrophy

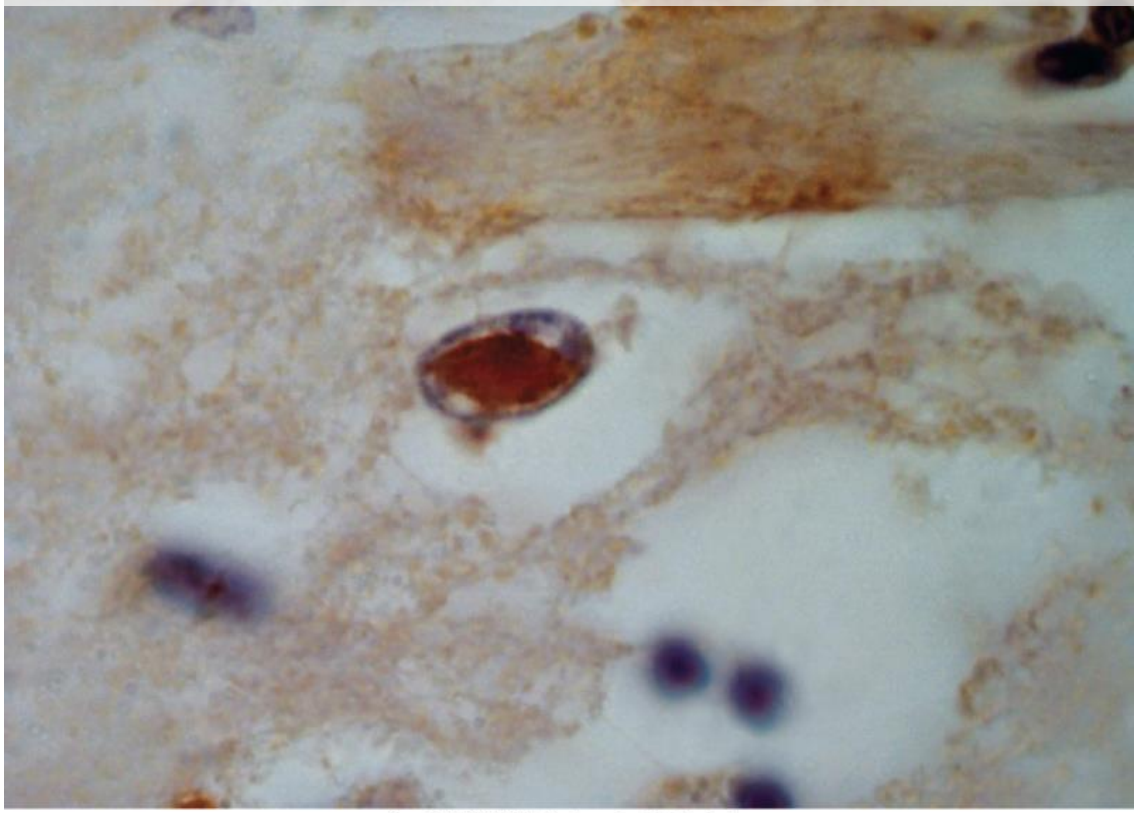
Normal **HD** **+/- Cortical atrophy (frontal)**

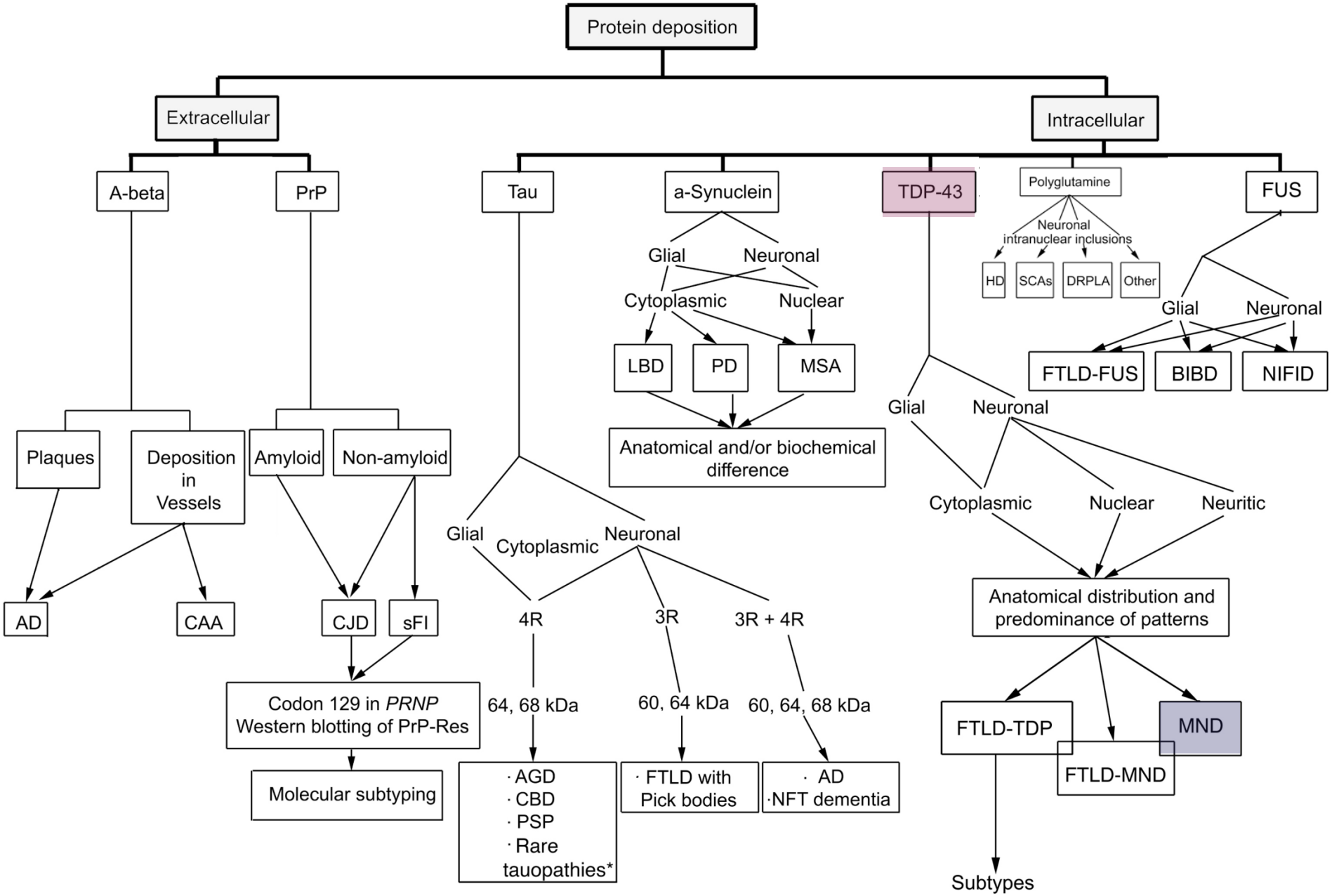




HD micro-morphology: Neuronal loss, gliosis, intranuclear inclusions

Ubiquitinated huntingtin protein
(ubiquitin immunostain)





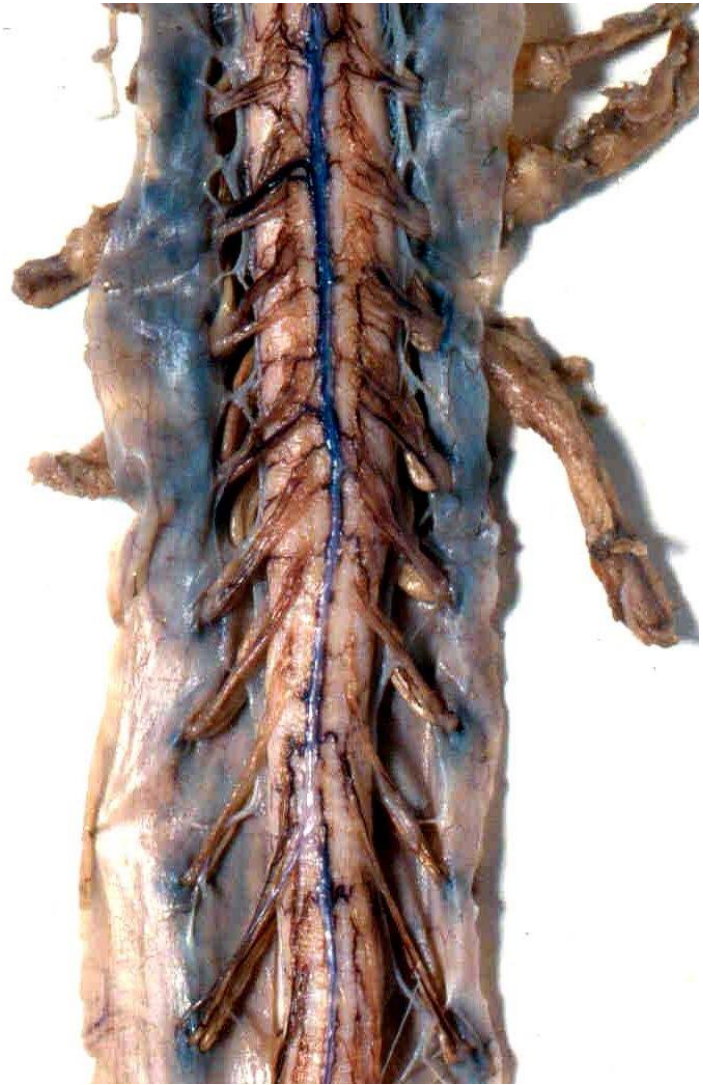
Kovács GG. et al. 2010 Acta Neuropath.

Amyotrophic Lateral Sclerosis (ALS)

- **Lower motoneurons get lost in brainstem and spinal cord → muscle atrophy, weakness, fasciculation**
- **Upper motoneurons get lost in primary motor cortex → paresis, hyperreflexia, spasticity**
- **40-70 ys; 1-2/100.000/y**
- **Sporadic**
- **Familial – 5-10%, e.g. C9orf72 hexanucleotide repeat expansion; SOD-1, TDP-43, FUS mutations**

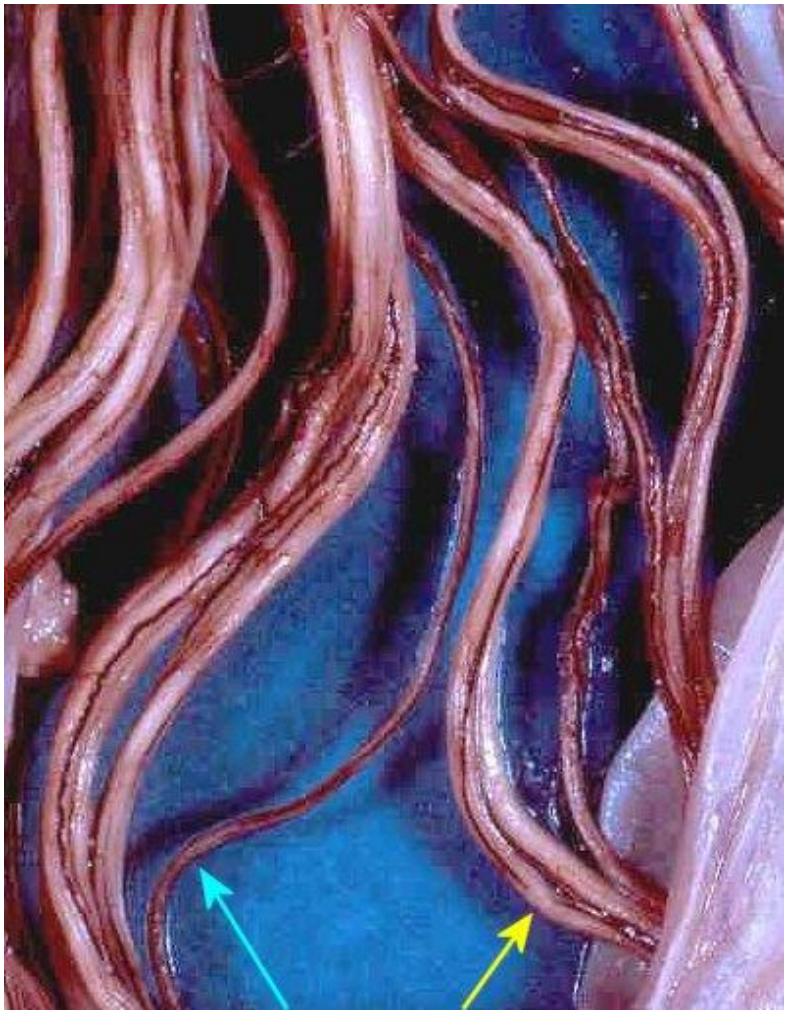
ALS – macro: atrophic and grey anterior nerves

Spinal cord front



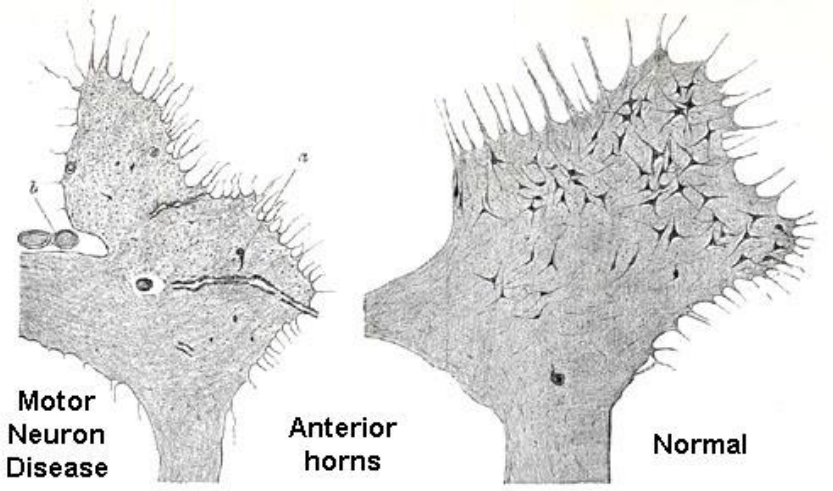
Spinal cord back

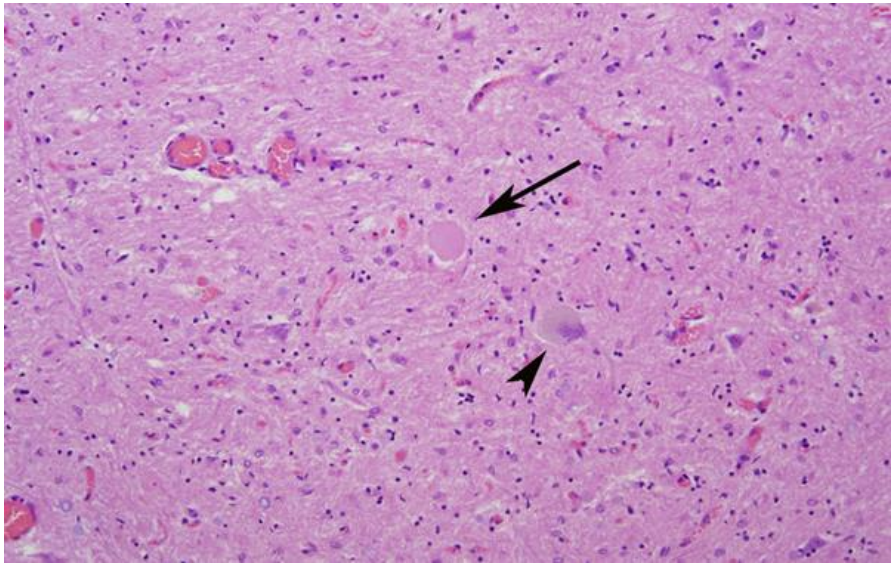
ALS – macro: atrophic and grey anterior nerves (cauda equina)

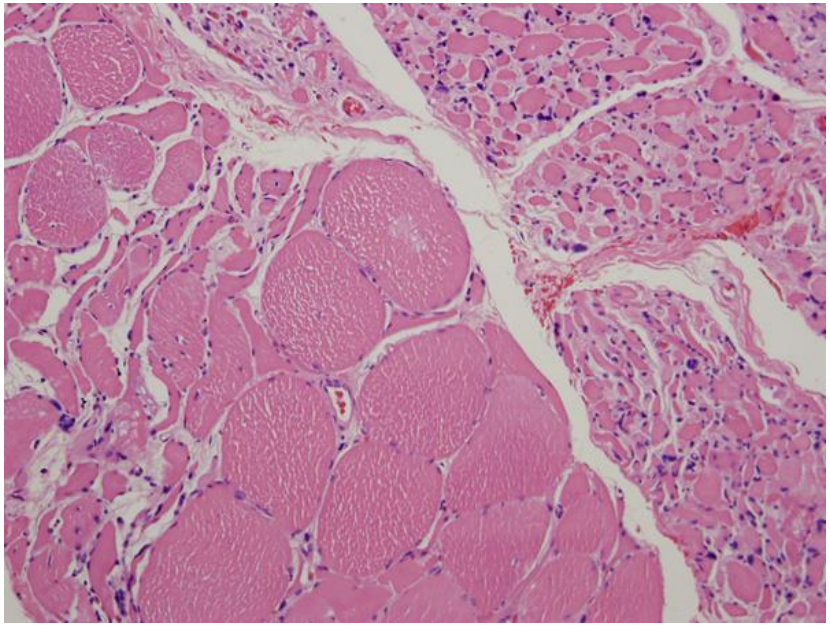


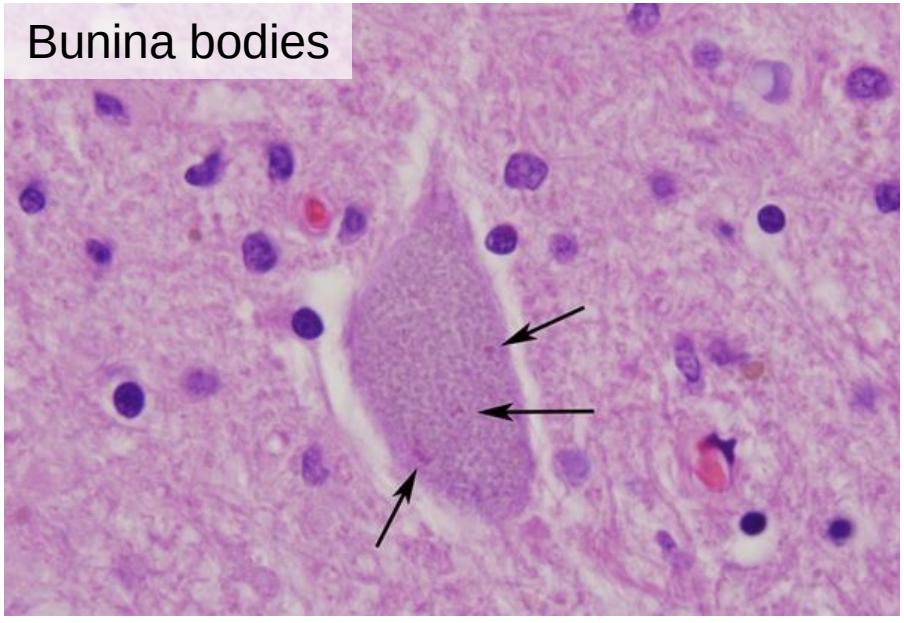
Anterior nerves Posterior nerves

ALS – micro: loss of motoneurons in spinal cord with gliosis, and muscle atrophy

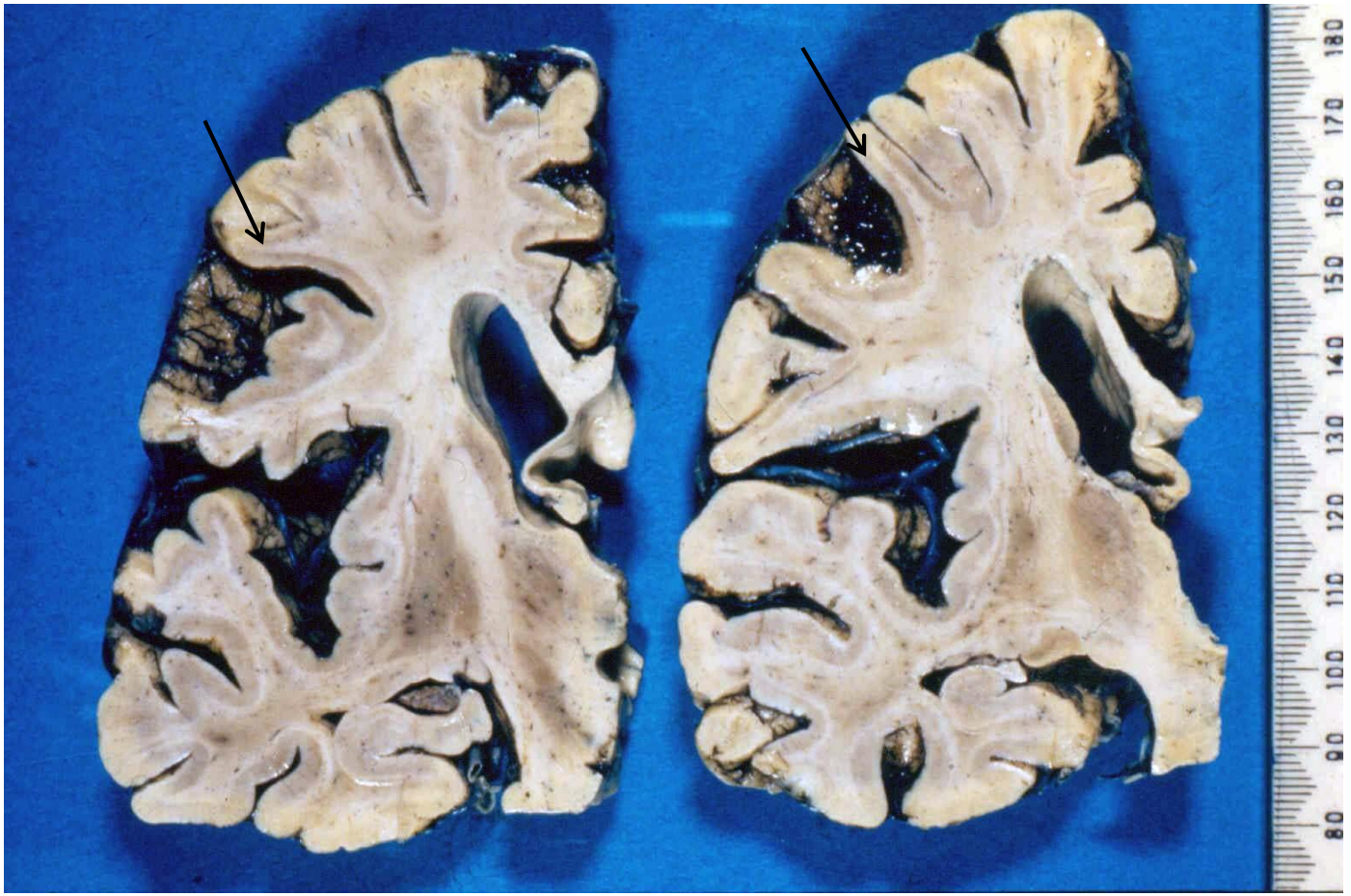




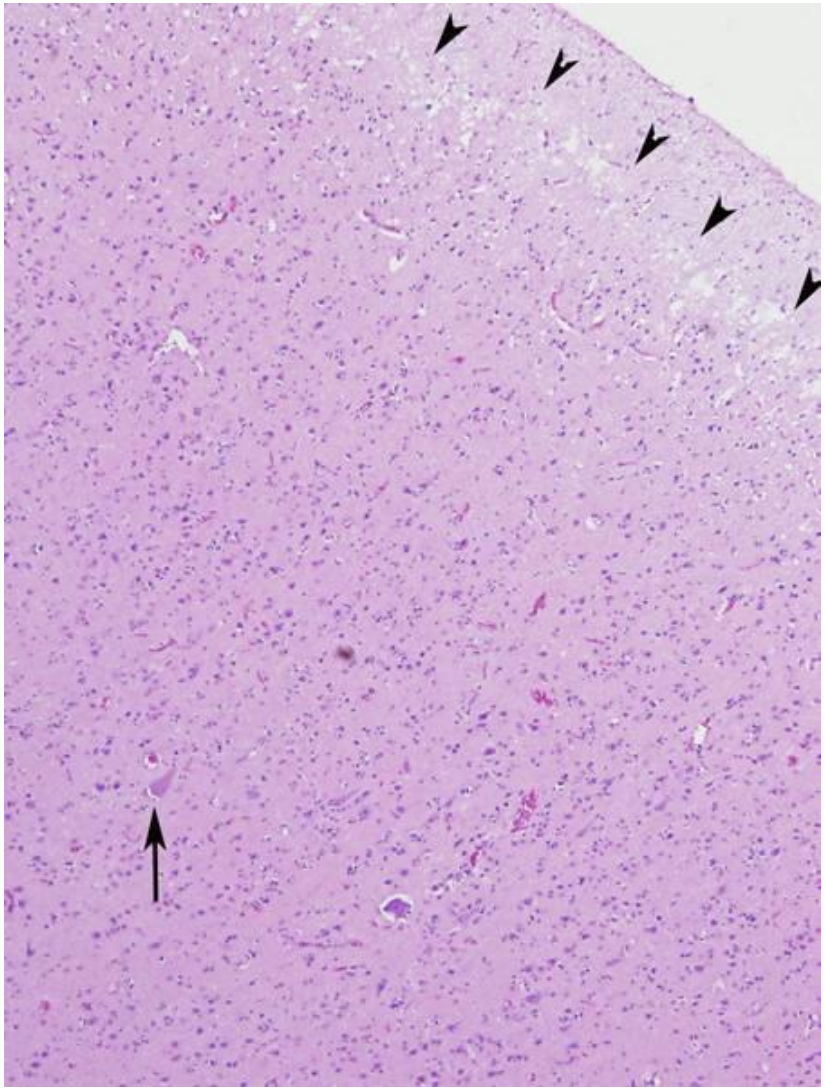


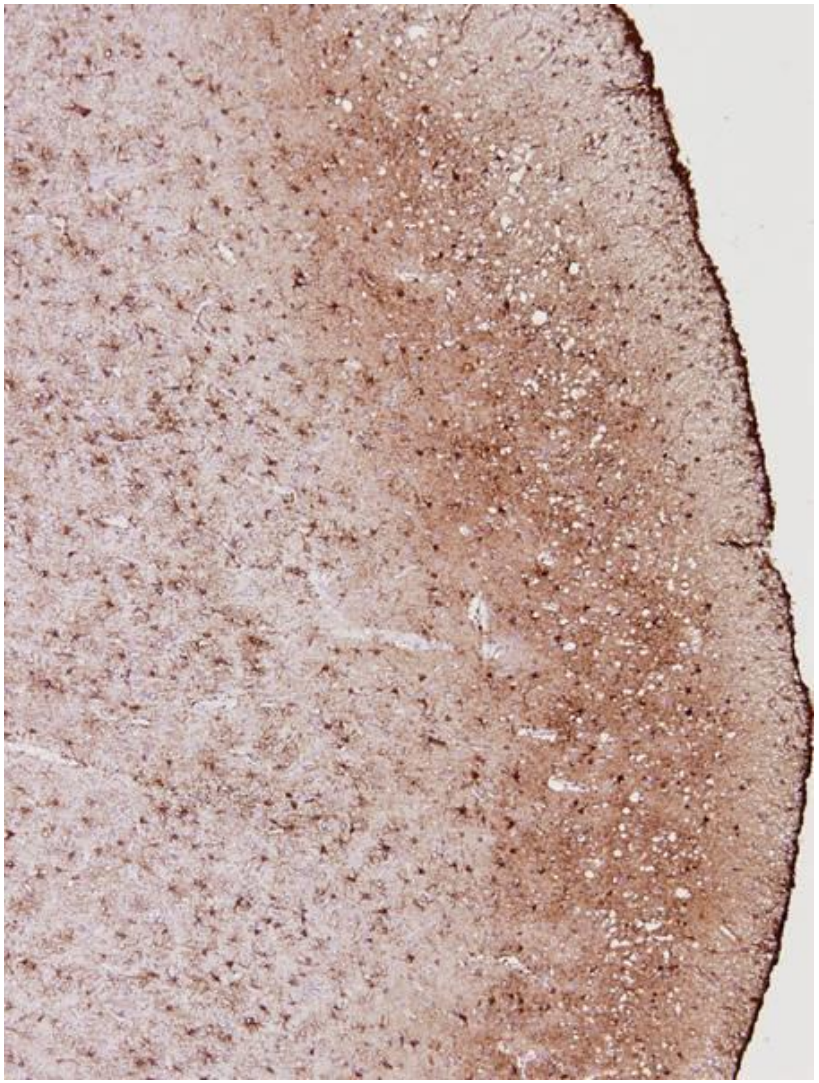


ALS – macro: motorcortex atrophy in severe cases



ALS – micro: neuronal loss, gliosis, spongiosis

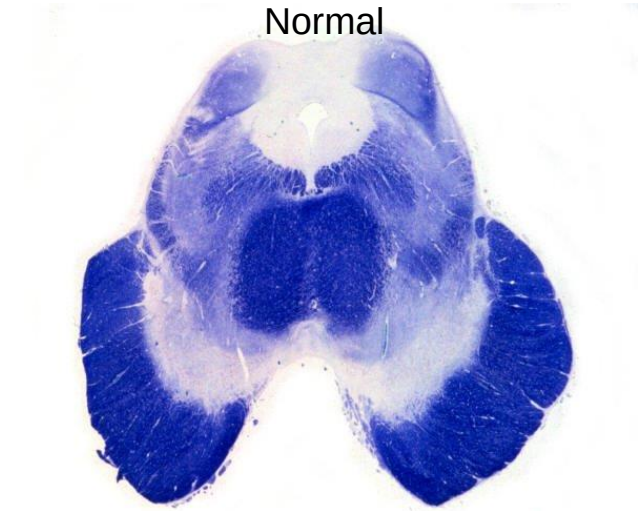


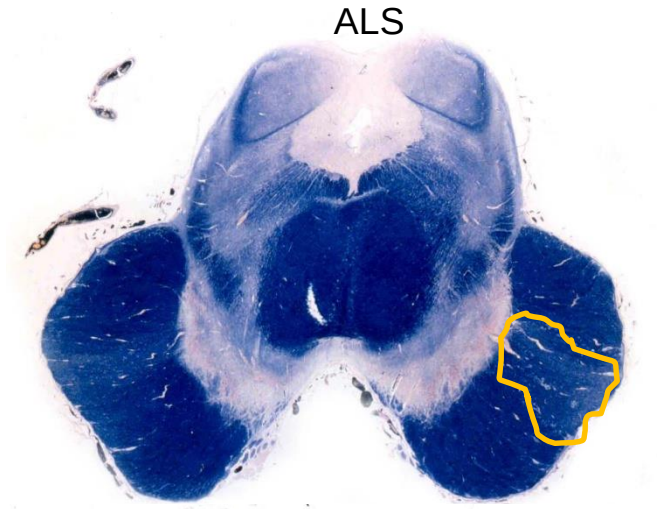


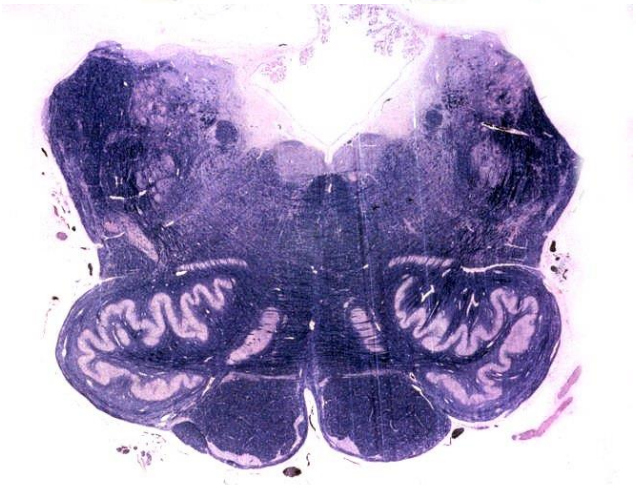
Due to loss of upper motoneurons corticospinal tract is degenerated

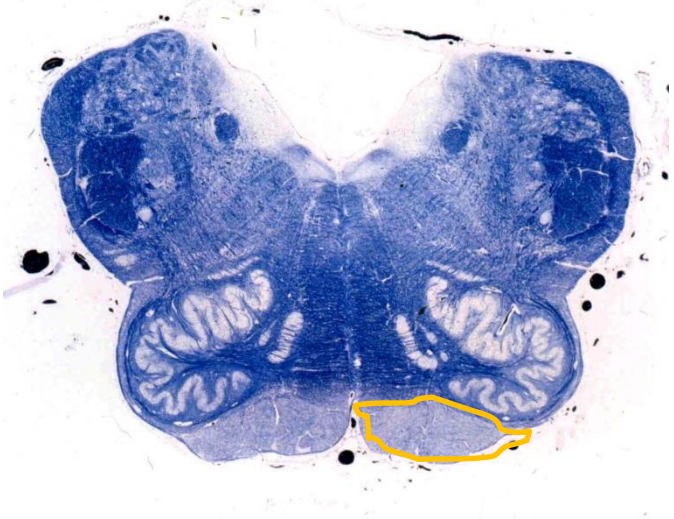
Normal

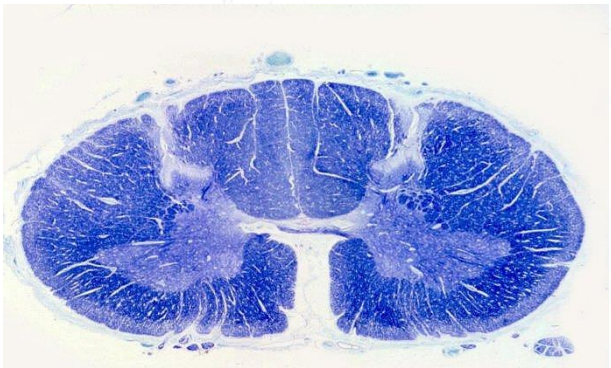
ALS

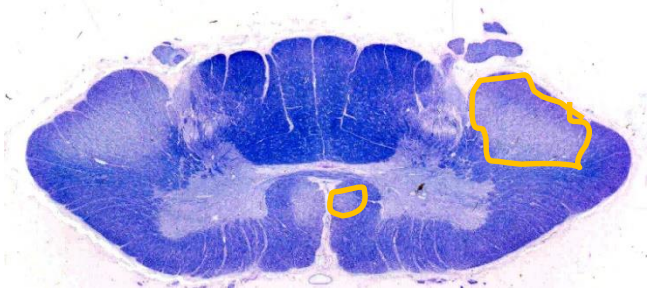






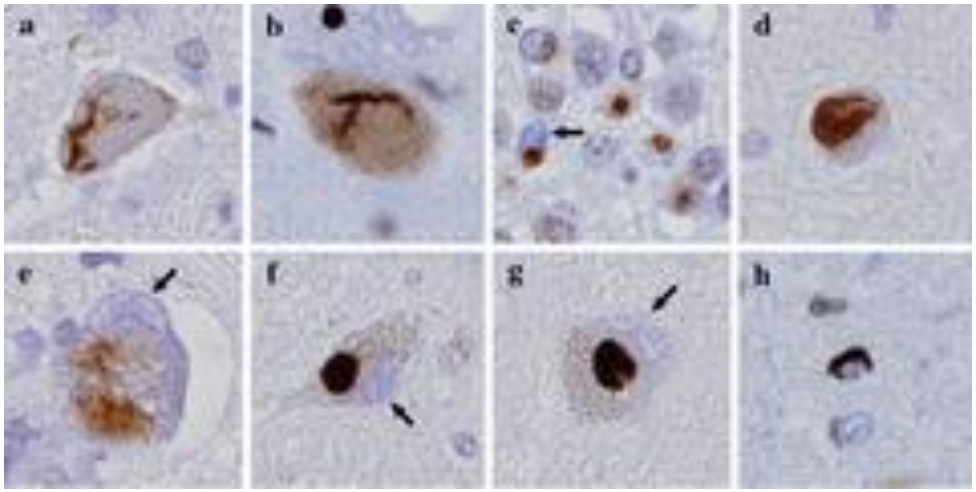


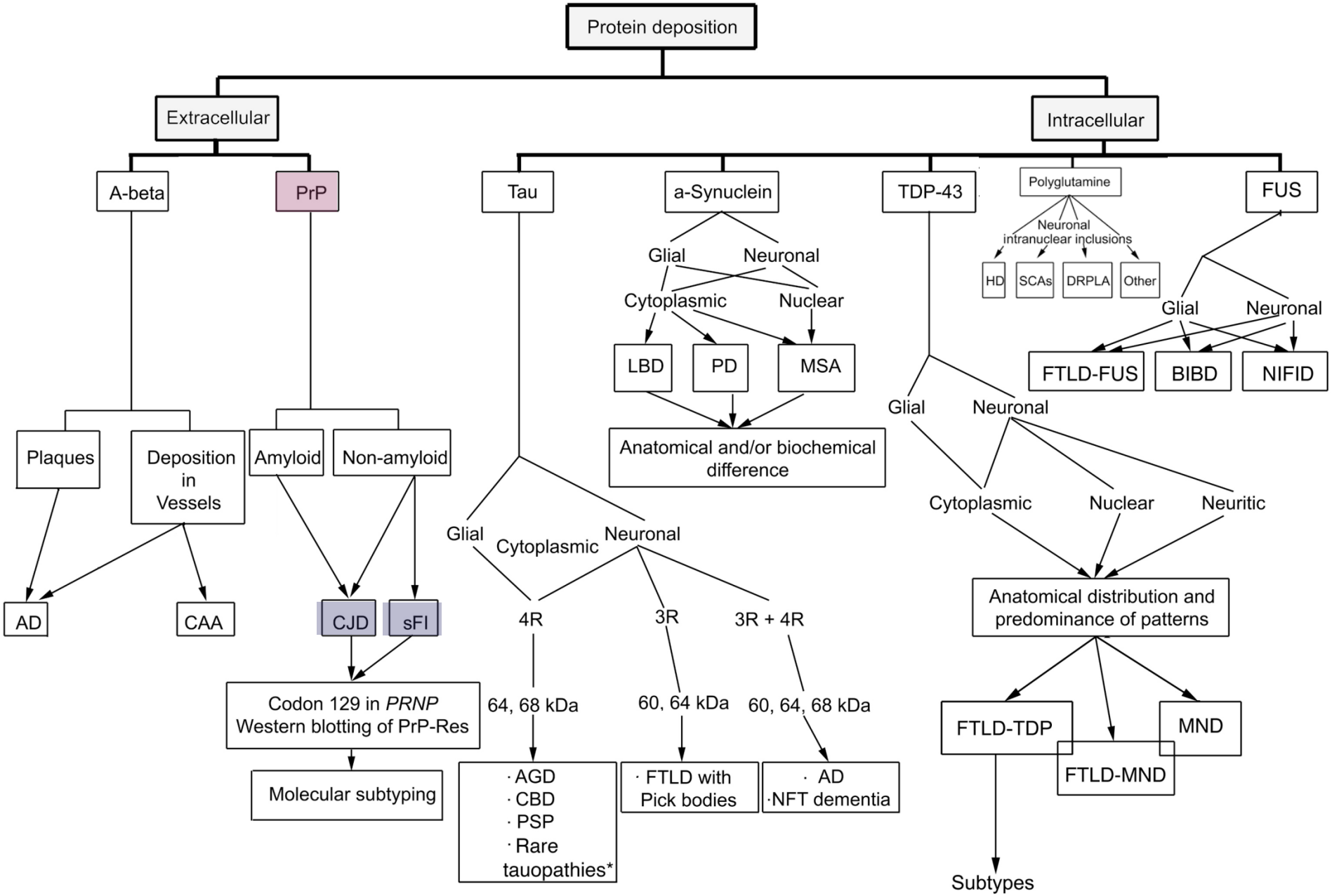




„lateral sclerosis”

ALS – TDP-43 positive neuronal and glial inclusions





Kovács GG. et al. 2010 Acta Neuropath.

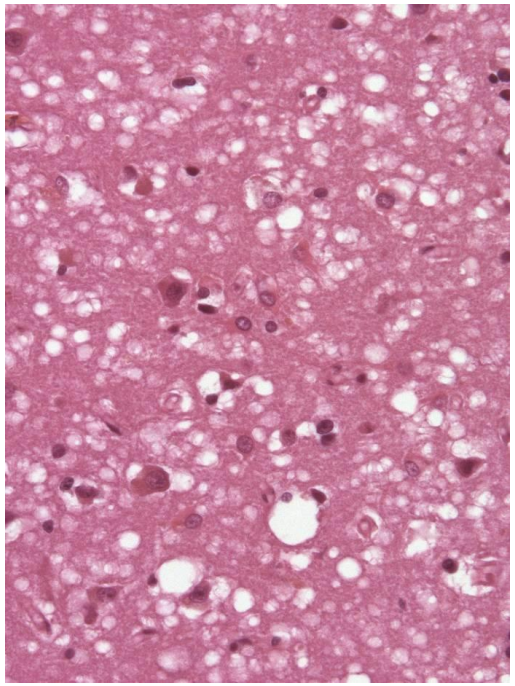
Prion disease
TSE – transmissible spongiform encephalopathies

1. Sporadic prion disease
   - Sporadic Creutzfeldt-Jakob disease (sCJD) – ~1/million/y
   - Sporadic fatal insomnia (sFI)
2. Inherited prion diseases (IPD) – PRPN gene mutation
   - Familial CJD (fCJD)
   - Gerstmann–Straussler–Scheinker syndrome (GSS)
   - Fatal familial insomnia (FFI)
3. Acquired prion disease – special groups are affected
   - Variant CJD (vCJD) – eating infected cattle
   - Iatrogenic CJD – growth hormon, cornea, electrodes etc.
   - Kuru - cannibalism

Prion disease – common features

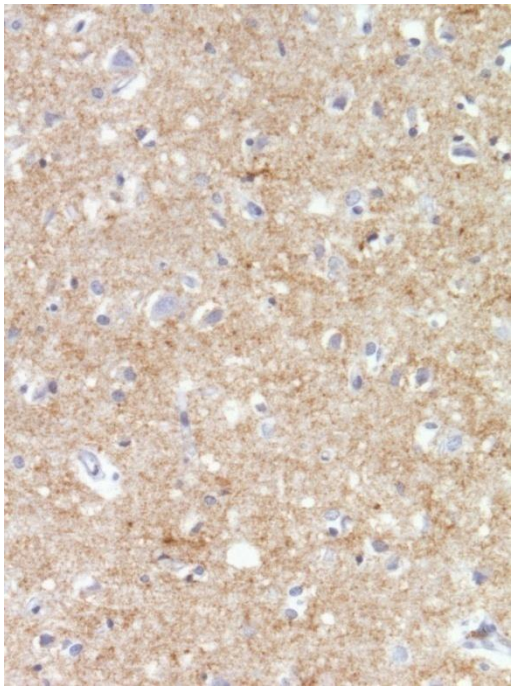
- **Progressive dementia**
- **Other neurological and psychiatric symptoms**
- **Fatal**

Neuronal loss
Spongiform degeneration



Reactive gliosis

PrP^{Sc} accumulation



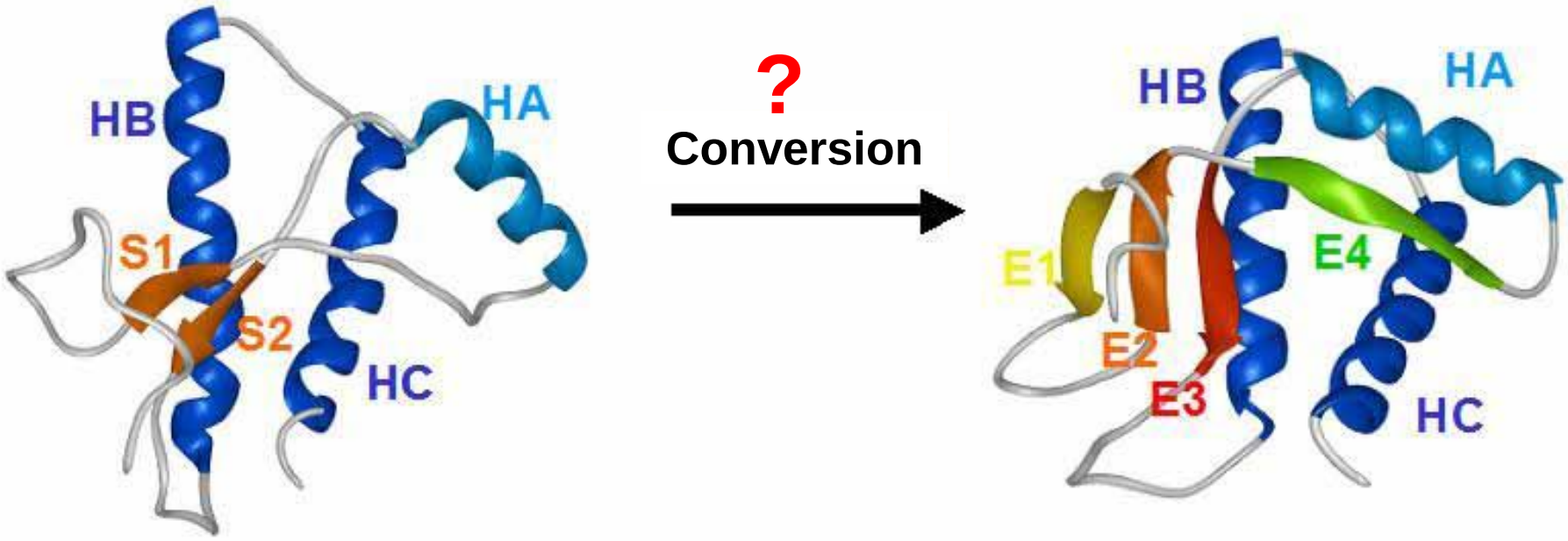
Pathomechanism of prion diseases

Normal: PrP^{c}

Mainly α-helix
protease sensitive
unknown function

Abnormal: PrP^{Sc}

Contains many β-sheet
protease resistant



Mechanisms for generation of PrP^{Sc}

Inherited forms

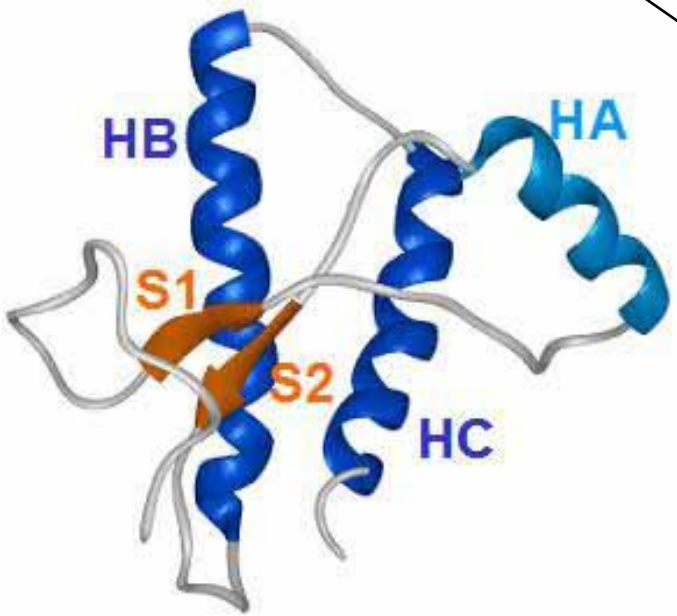
The nature of protein is different due to mutation – ↑ propensity to convert

sCJD

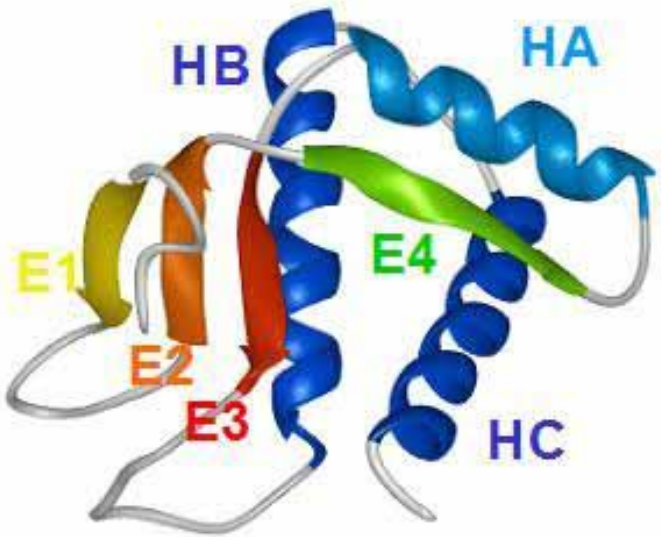
Thought to be age related: Abnormal posttranslational modification processes, „quality control” disturbance

Iatrogenic CJD

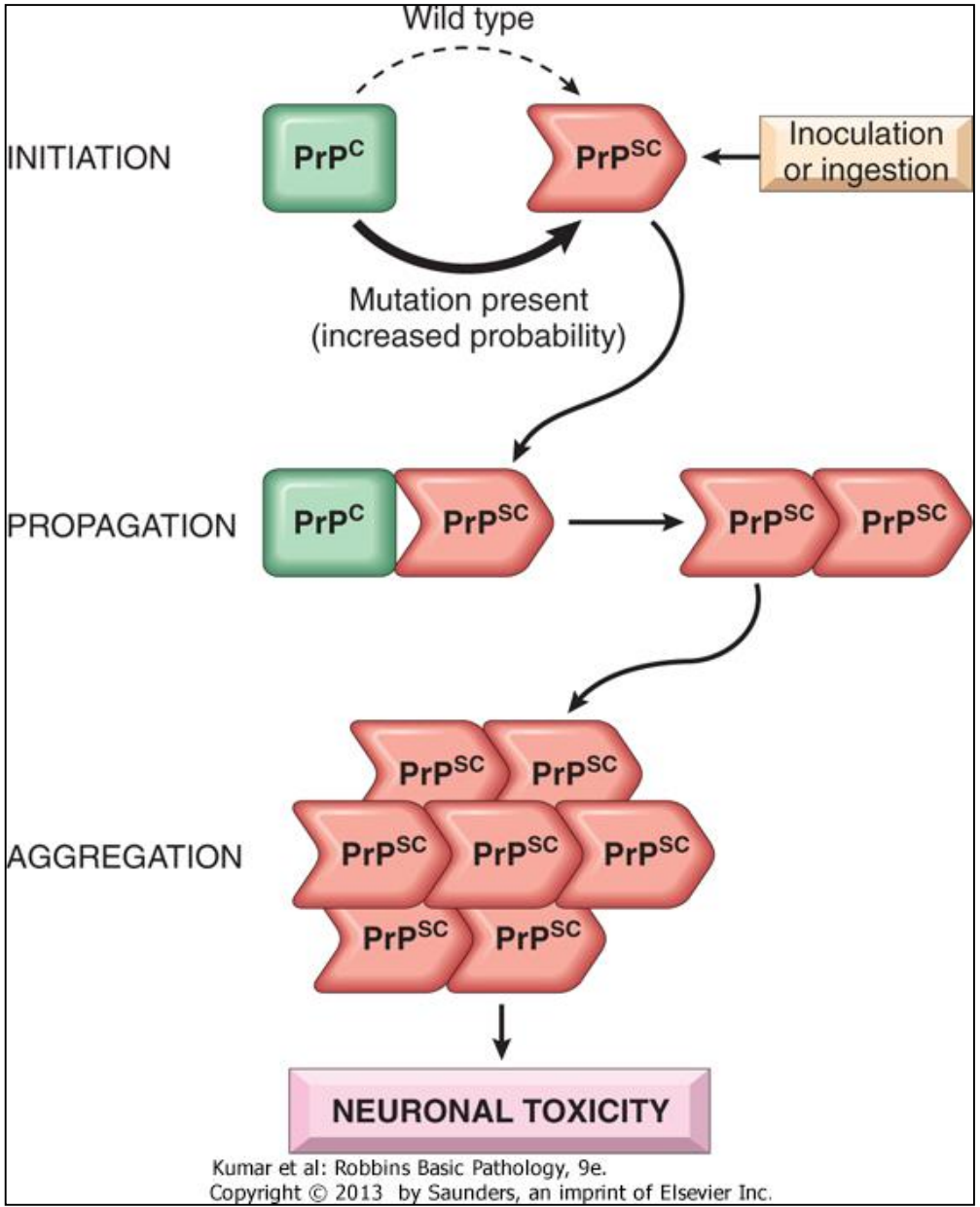
Exogene PrP is abnormal



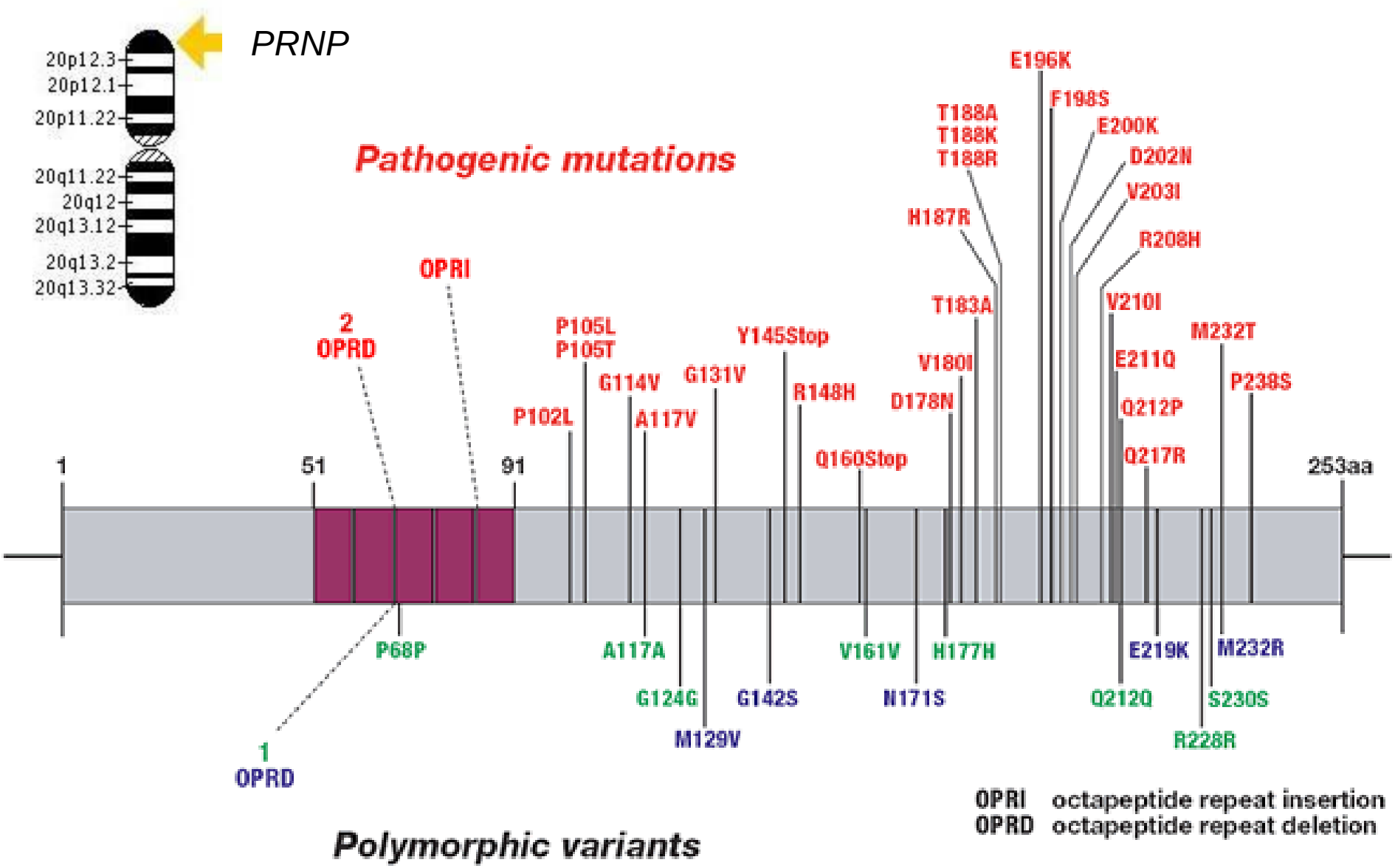
Conversion



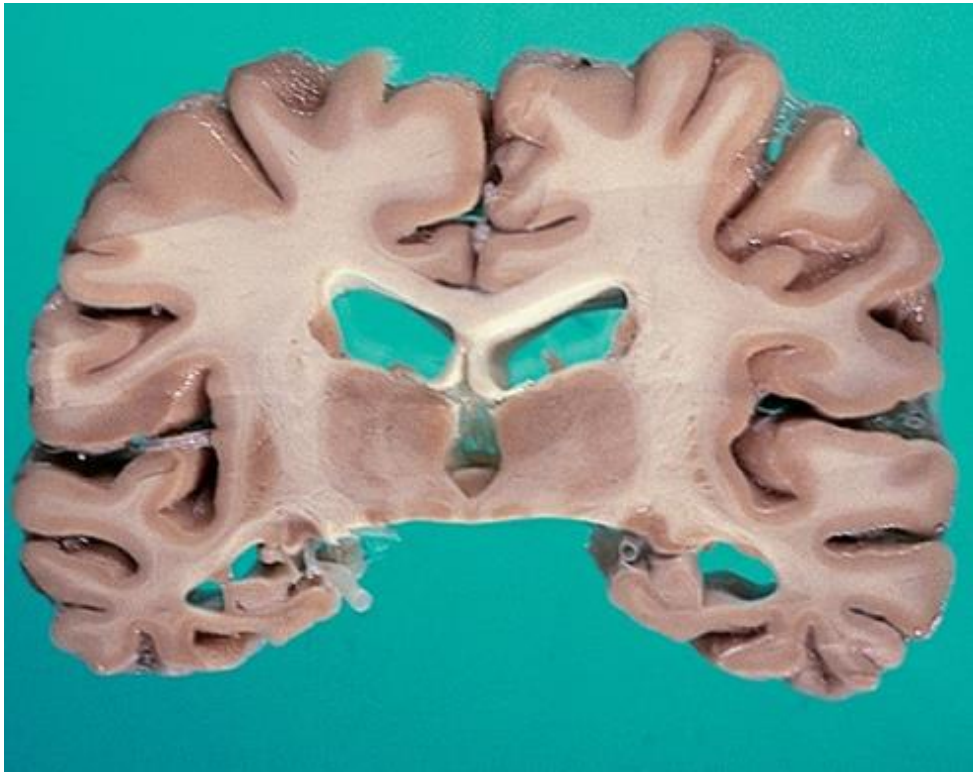
Pathogenesis of prion diseases

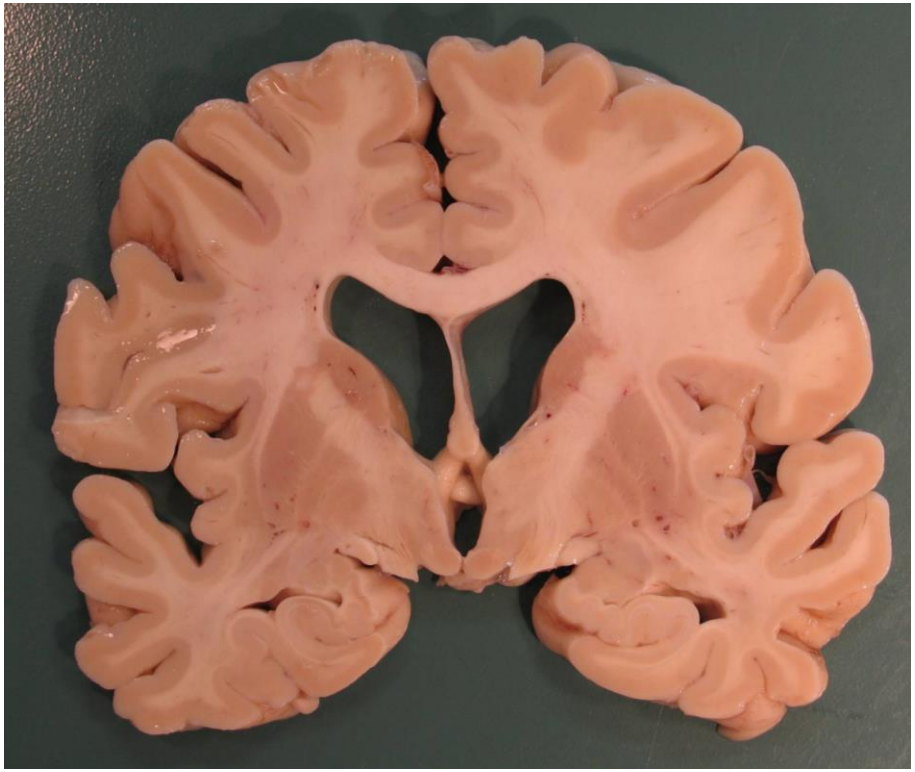


Prion protein gene - *PRNP*



Prion disease – macro: atrophic or normal brain

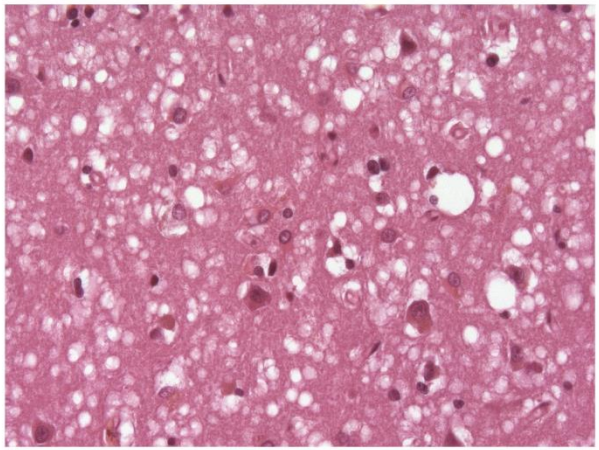


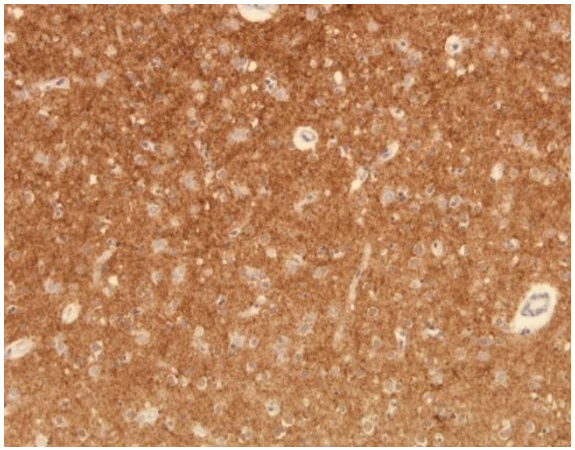


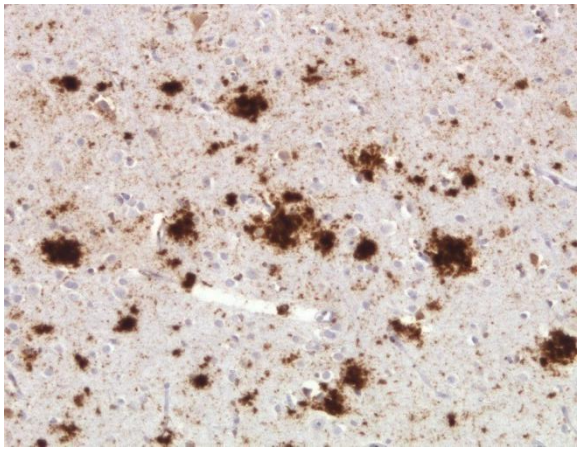
Prion disease – micro: „Spongiform change” and PrP^{Sc} accumulation

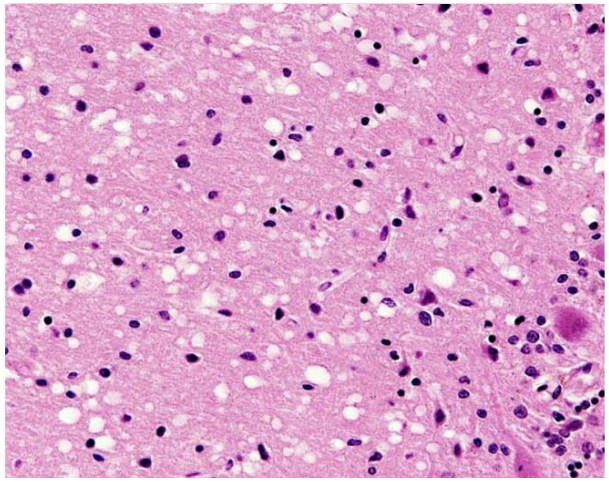
Spongiform degeneration

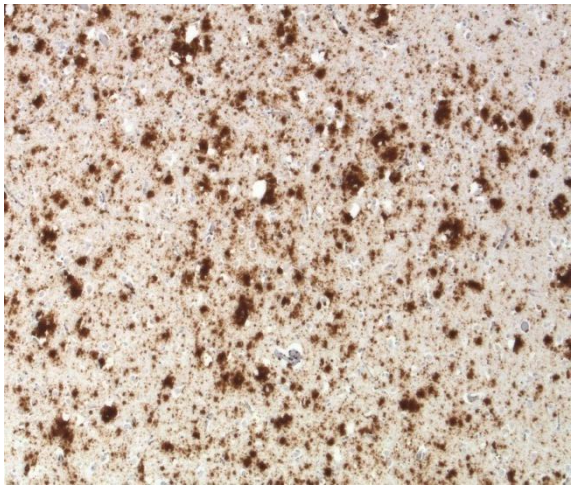
Abnormal PrP

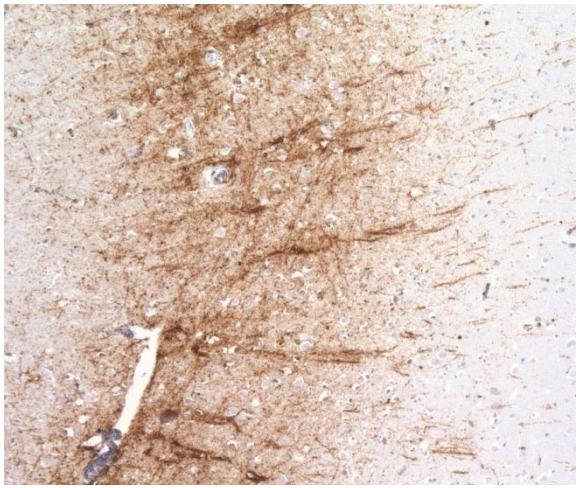












Prion disease – micro: vCJD