NSCI 2100 - Human Neuroanatomy

Neurodegenerative Diseases

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Driven to Discover℠

Objectives of the lecture(s)

1. To learn general notions of neurodegenerative diseases and to describe their clinical presentations

2. To understand what differentiates genetic and sporadic forms of neurodegenerative disorders

3. To learn the potential mechanisms underlying a subset of neurodegenerative diseases

Lecture Outline

I. Introduction:

- A. What are neurodegenerative disorders?
- B. Types of neurodegenerative diseases
- C. Brain structures affected in neurodegenerative diseases
- D. Protein aggregation & neurodegenerative diseases

II. Alzheimer's disease:

III. Frontotemporal lobar degeneration:

IV. Parkinson's disease:

V. Amyotrophic lateral sclerosis:

VI. Trinucleotide repeat expansion diseases:

- A. Huntington's disease
- B. Other disorders

I. A. What are Neurodegenerative disorders?

Characterized by progressive **dysfunction** and death of neurons

Degeneration often affects specific systems, implying selective vulnerability

Abnormal accumulation(s) of specific proteins in the brain

Pathophysiology is poorly understood:

- **Aging** is generally the most important risk factor
- Interaction between **genetic and environmental factors**
- **Genetic** & **sporadic** forms

I.B. Types of neurodegenerative diseases

Cognitive disorders

Degeneration affects the cerebral cortex, leading to *dementia*.

Alzheimer's disease (AD), Frontotemporal dementia (FTD), Pick's disease

Motor disorders

1- Degeneration affects motor neurons, leading to *motor weakness*.

Amyotrophic Lateral Sclerosis (ALS), spinal muscular atrophy (SMA)

2- Degeneration affects cerebellum & tracts, leading to *Cerebellar ataxia*.

Friedreich ataxia (FA), ataxia-telangiectasia (AT)

3- Degeneration affects substantia nigra & basal ganglia, leading to *akinetic & rigid movements*.

Parkinson's disease (PD), Progressive supranuclear palsy (PSP)

4- Degeneration affects basal ganglia, leading to *hyperkinetic movements*.

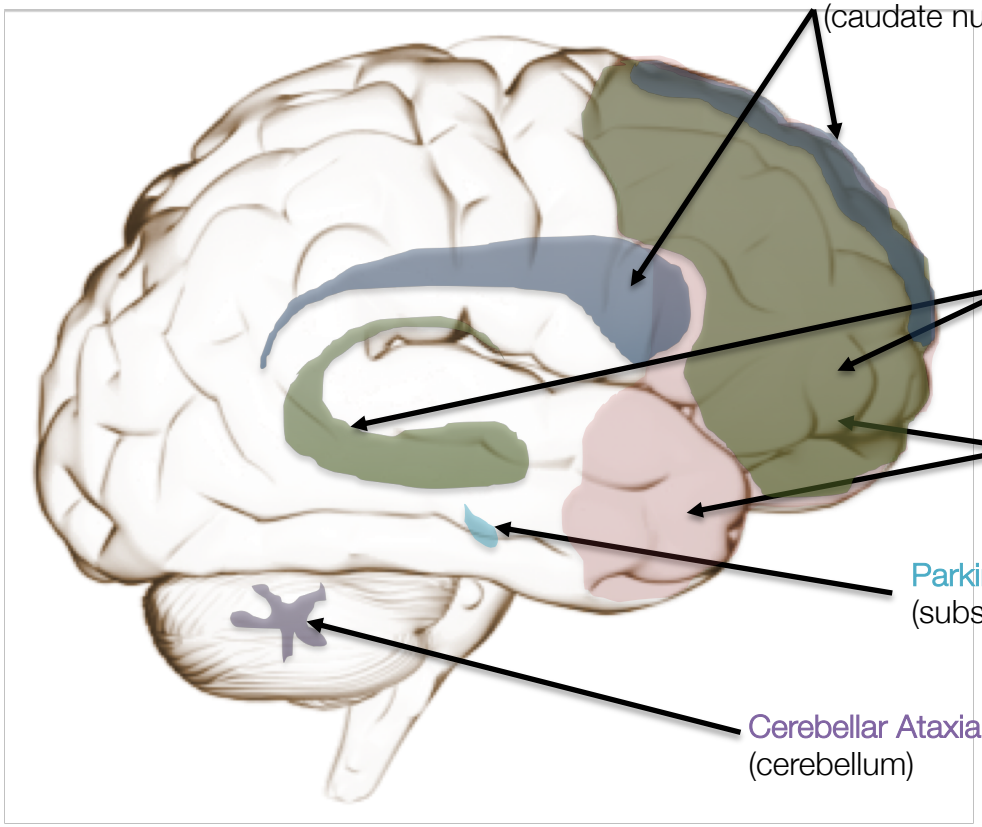
Huntington's disease (HD)

Sensory disorders

Degeneration affects the sensory neurons, leading to *loss of senses*

Retinitis pigmentosa (RP)

I. C. Brain structures affected in neurodegenerative diseases



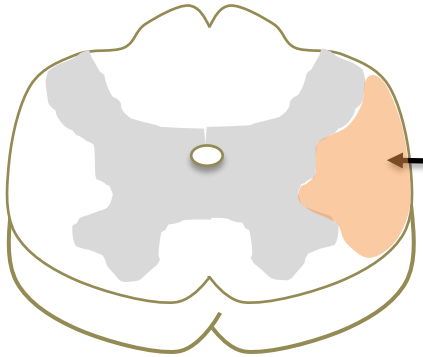
Huntington's disease
(caudate nucleus, striatum & frontal cortex)

Alzheimer's disease
(Hippocampus, entorhinal & frontal cortex)

Frontotemporal lobar degeneration
(frontal and temporal cortex)

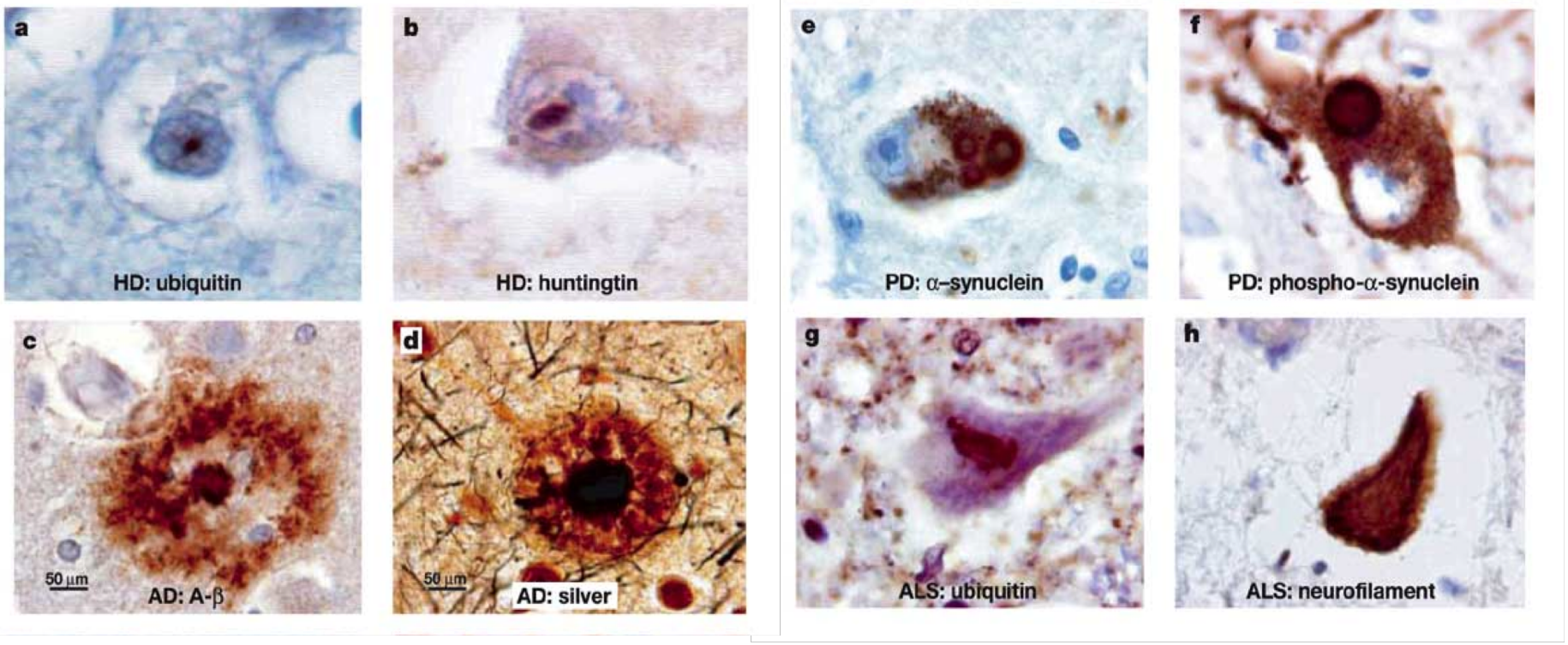
Parkinson's disease
(substantia nigra)

Cerebellar Ataxia
(cerebellum)



Amyotrophic Lateral Sclerosis
(motor neurons)

I.D. Neurodegenerative disease and protein aggregation



nature medicine

Ross & Poirier (2004) Nat Med, **10 Suppl**:S10-7.
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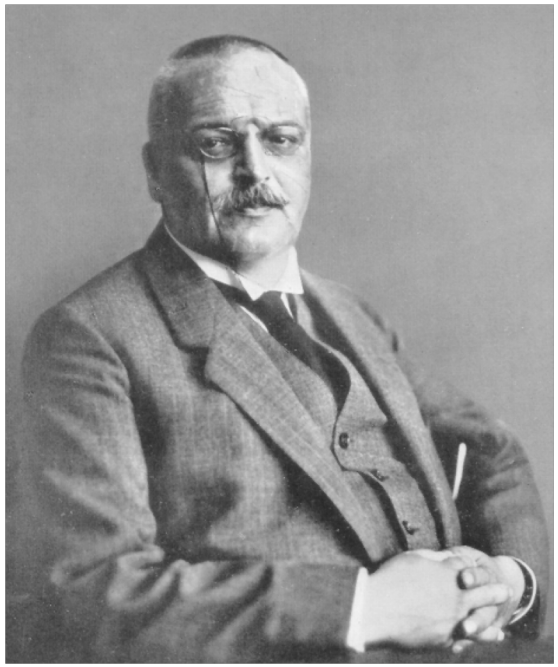
II. Alzheimer's Disease (AD)

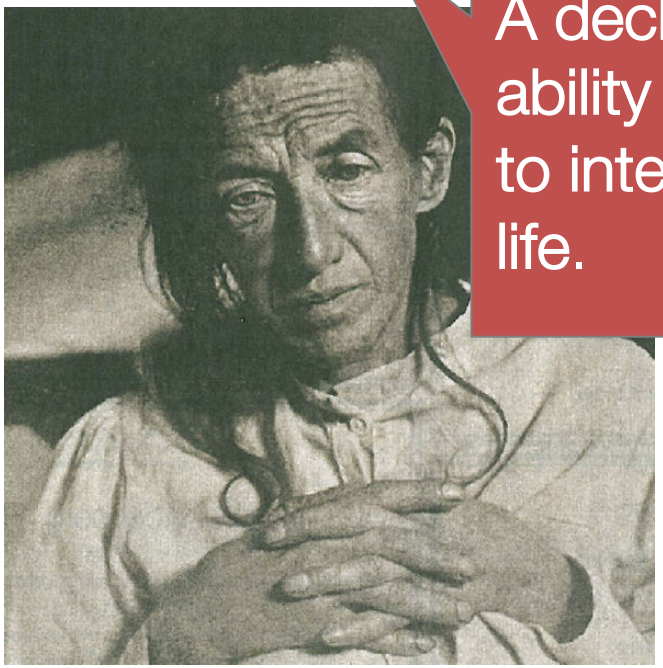
II. A. Definition:

- Progressive neurodegenerative dementia, whose duration of the disease can vary from 3 year to 20 years (after clinical manifestation).

- Most common type of dementia in the elderly.



Alois Alzheimer (1909)



Auguste D. (1901)

A decline in mental ability severe enough to interfere with daily life.

© Archive for History of Psychiatry, Department of Psychiatry University of Munich.

II. B. classification:

98%
Sporadic

Late Onset AD

2%
Familial

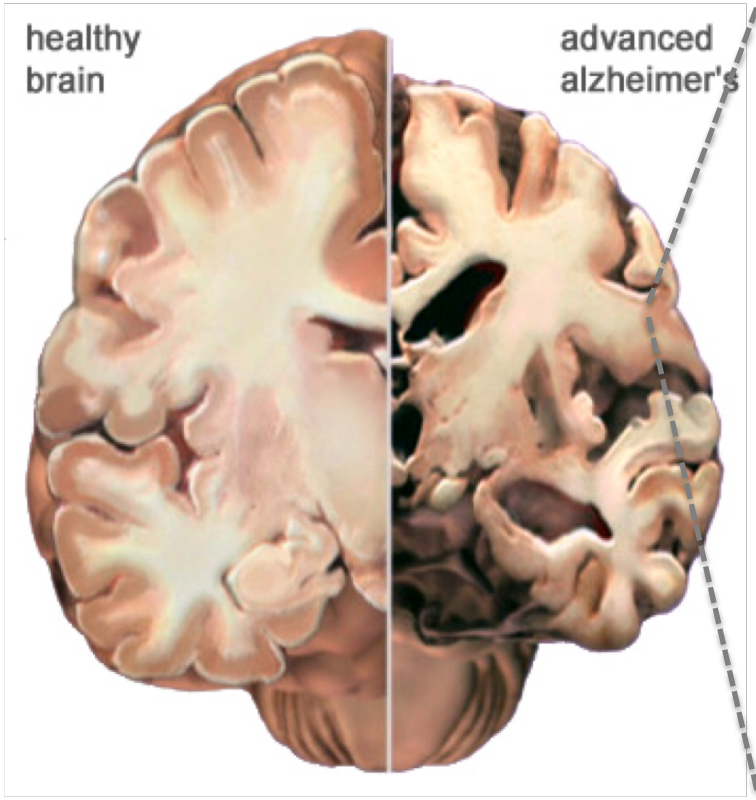
- *APP* (Chr. 21)
- *PSEN1* (Chr. 14)
- *PSEN2* (Chr. 1)

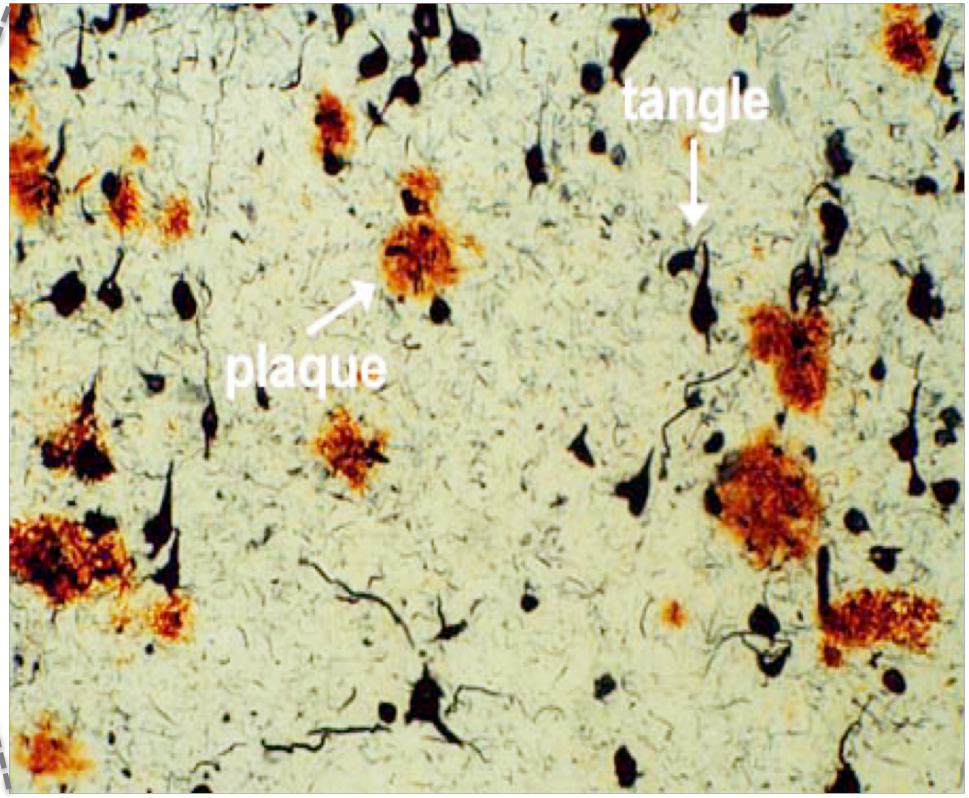
Early Onset AD

II. C. Histopathological features of Alzheimer's Disease

Macroscopic

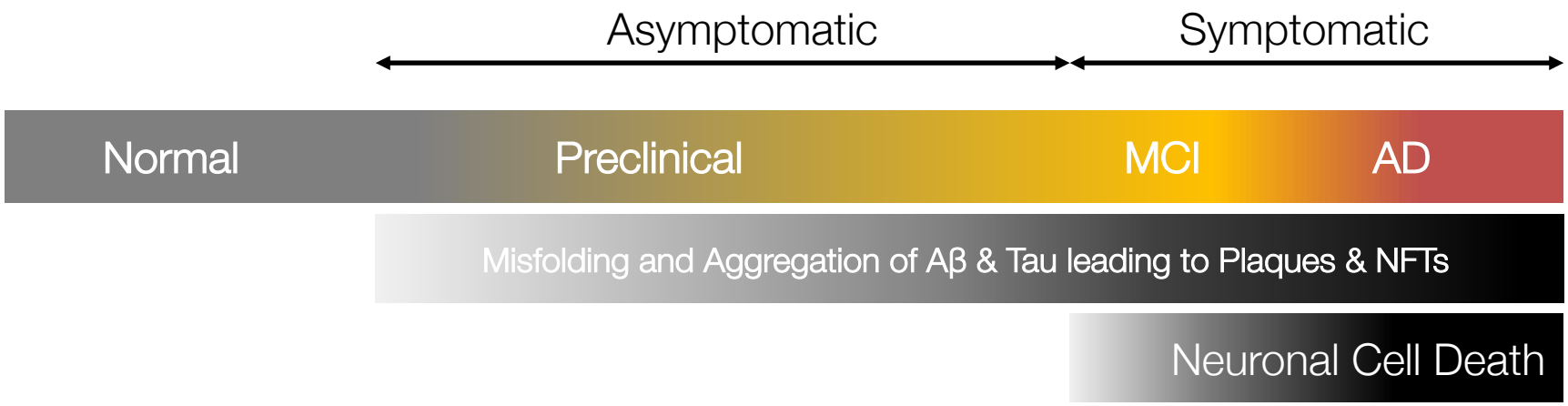
Microscopic





Extracellular accumulation of amyloid-beta (Aβ) in *amyloid plaques* and intracellular accumulation of tau inclusions forming *neurofibrillary tangles* constitute invariant pathological hallmarks of Alzheimer's disease.

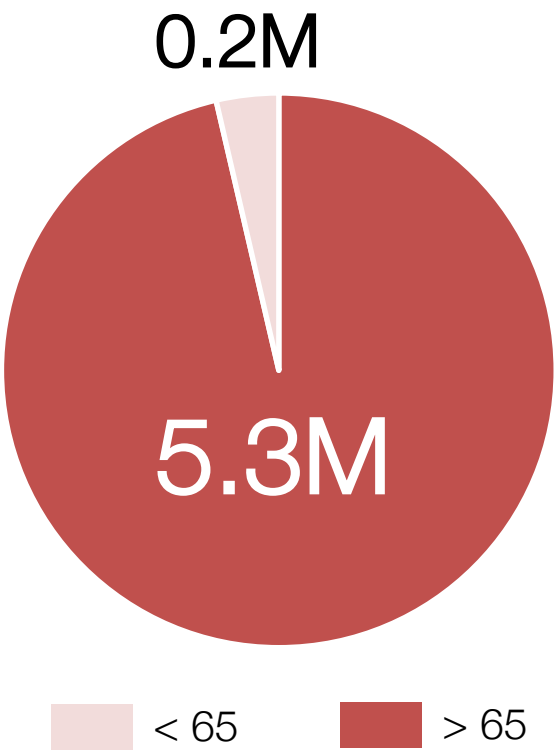
II. D. Symptoms of Alzheimer's Disease:

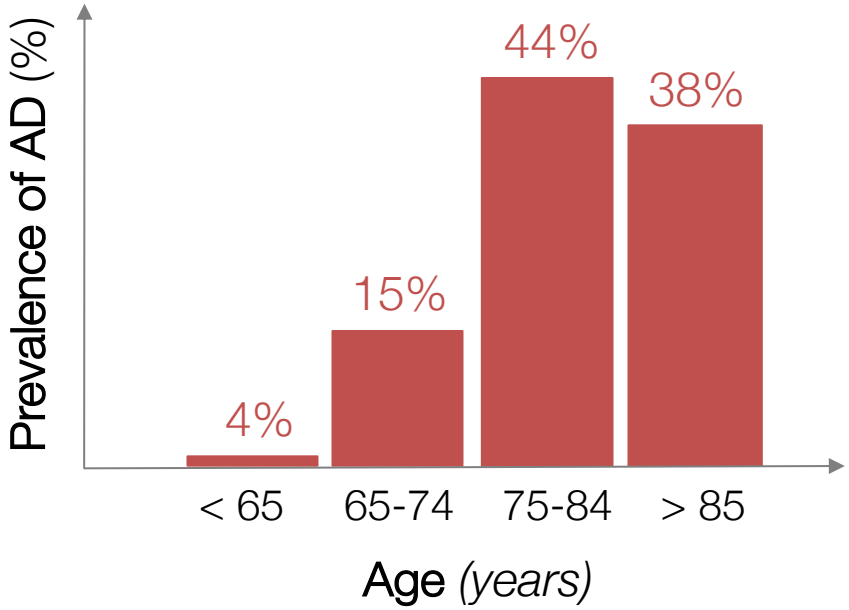


The clinical presentation varies with the stage of AD

- Memory loss that disrupts daily life
- Challenges in planning or solving problems
- Confusion with time or place
- Trouble with visual and spatial
- New problems with word finding and speaking
- Decreased or poor judgment
- Changes in mood or personality

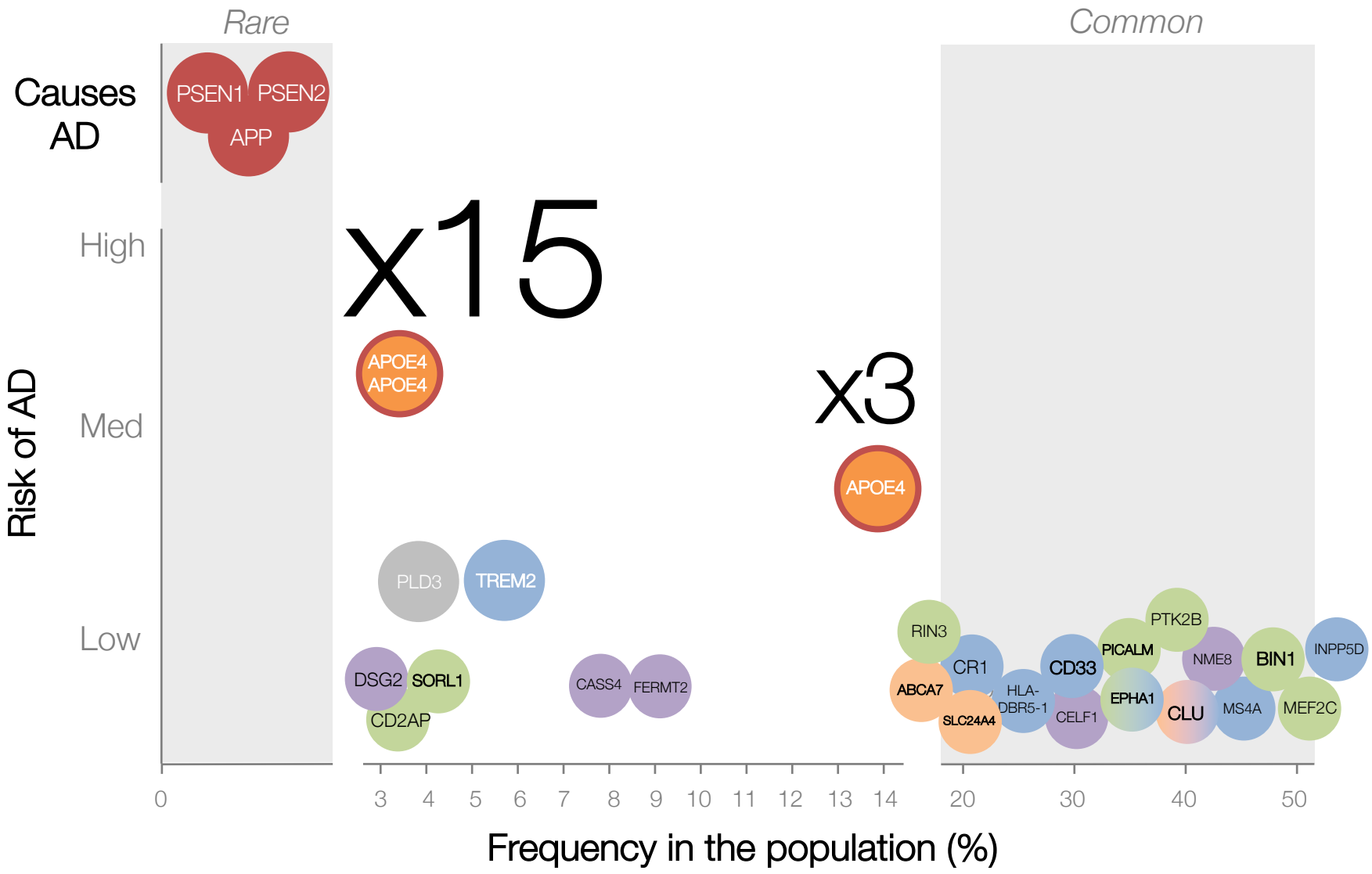
II. E. Aging and Alzheimer's disease:





Adapted from
Hebert *et al.*, 2013 (*Neurology*)
© 2013 The American Academy of Neurology

II. F. Genetic variants of Alzheimer's disease:



Adapted from
Karch & Goate, 2014 (*Biol. Psych.*)
© 2014 The Society of Biological Psychiatry

II. G. Treatments

Cholinesterase inhibitors
- Donezepil (Aricept®)
- Rivastigmine (Excelon®)
- Galantamine (Razadyne®)

NMDA receptor antagonists
- Memantine-HCl (Namenda®)

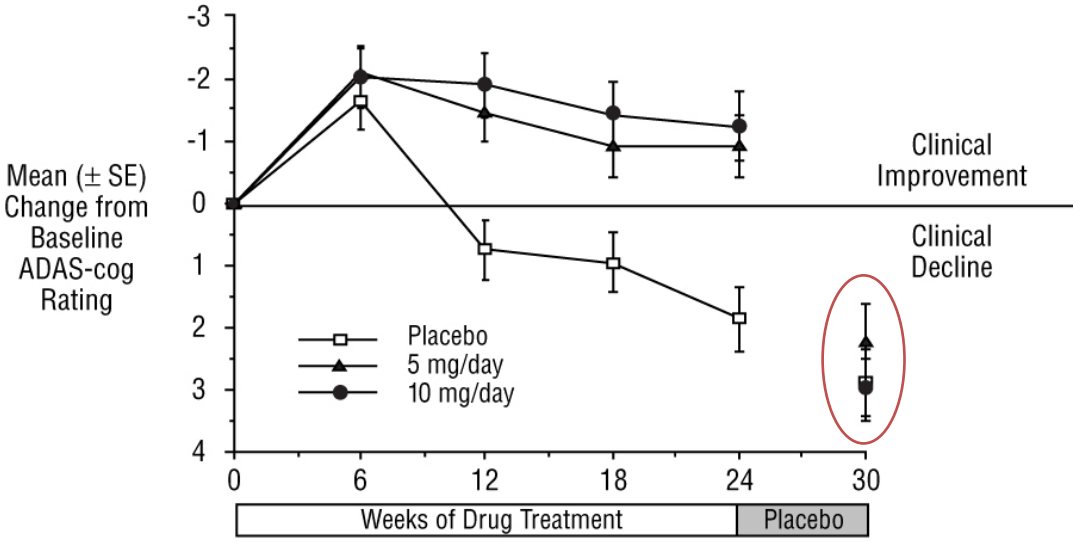


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment.

III. Frontotemporal dementia (FTD)

III. A. Definition:

Frontotemporal dementia (FTD) defines a large group of **clinically, pathologically and genetically heterogeneous disorders associated with atrophy in the frontal lobe and temporal lobe** of the brain.

Because disease onset occurs before 65 years of age in ~75-80% of cases, FTD is considered a **pre-senile dementia**.

- **2nd most common cause of early-onset dementia** after Alzheimer's disease.
- **4th most common cause of dementia** after Alzheimer's disease, dementia with Lewy bodies and vascular dementia *(> 65 yr-old)*.

Frontotemporal lobar degeneration (FTLD) is the pathological term for the clinical syndrome *Frontotemporal dementia (FTD)*.

The symptoms of FTD and Alzheimer might overlap.

III. B. Classification:

75%
Sporadic

Late Onset FTD

25%
Familial

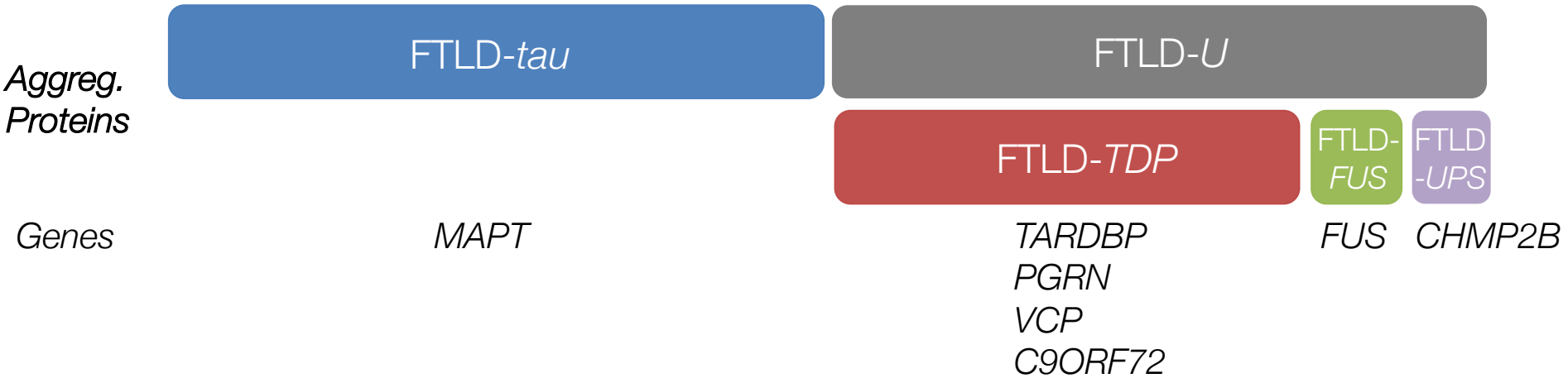
- *MAPT (microtubule associated protein tau)*
- *TARDBP (TDP-43)*
- *FUS (fused in sarcoma)*
- *CHMP2B (charged multivesicular protein 2B)*
- *C9orf72 (chromosome 9 open reading frame 72)*

Early Onset FTD

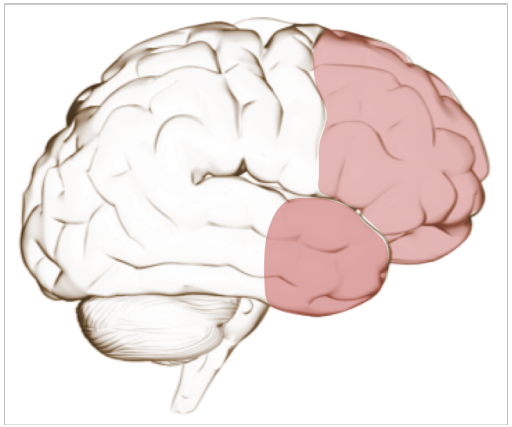
Sporadic FTLD is associated with risk factors, notably **aging (>40-65 yrs)**

III. C. Subtypes:

FTLD subtypes into broad categories, *based on the molecular defect that is currently felt to be most characteristic* (FTLD-*protein*).



III. D. Symptoms of FTD:



The clinical presentation varies with the type of FTD

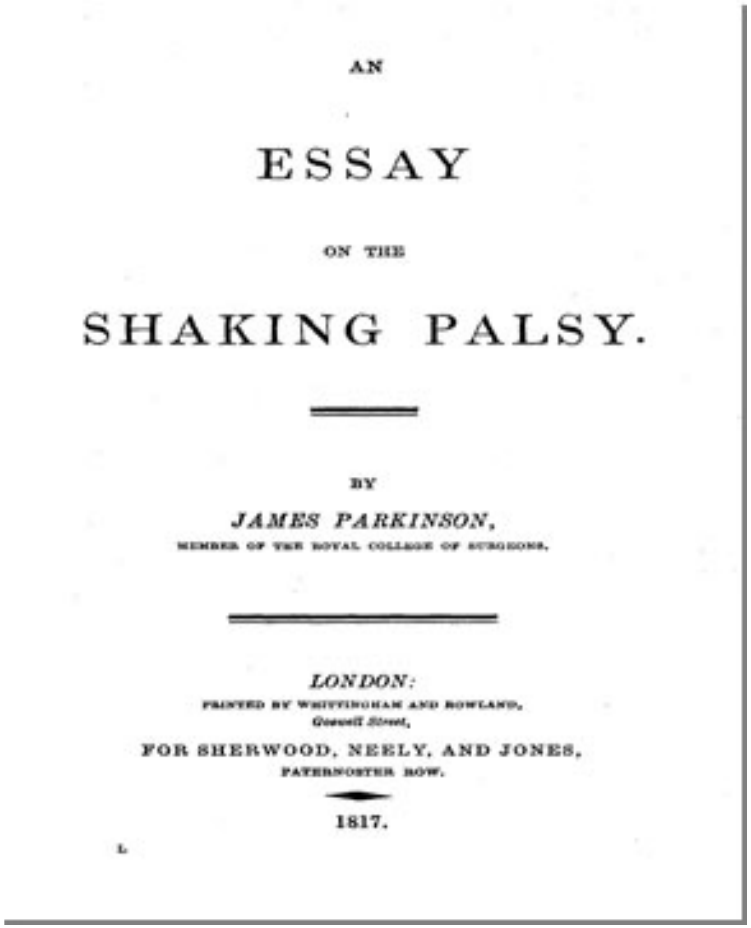
- extreme changes in behavior and personality
- impairment or loss of speech and language difficulties
- Movement impairments (rarer)

IV. Parkinson's Disease (PD)

IV. A. Definition:

Parkinson's disease (PD) belongs to a group of conditions called *motor system disorders*, which are the result of the **loss of dopamine-producing brain cells in the substantia nigra** (>50-70%).

Named after the English physician **James Parkinson**, who described the disorder in "An Essay on the Shaking Palsy" in **1817**.



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

IV. B. Classification:

95%
Sporadic

Late Onset PD

5%
Familial

- *SNCA (alpha-synuclein)*
- *Parkin*
- *DJ-1*
- *PINK1 (PTEN-induced kinase 1)*
- *LRRK2 (Leucine-Rich Repeat Kinase 2)*
- *Duplication or triplication of SNCA locus*

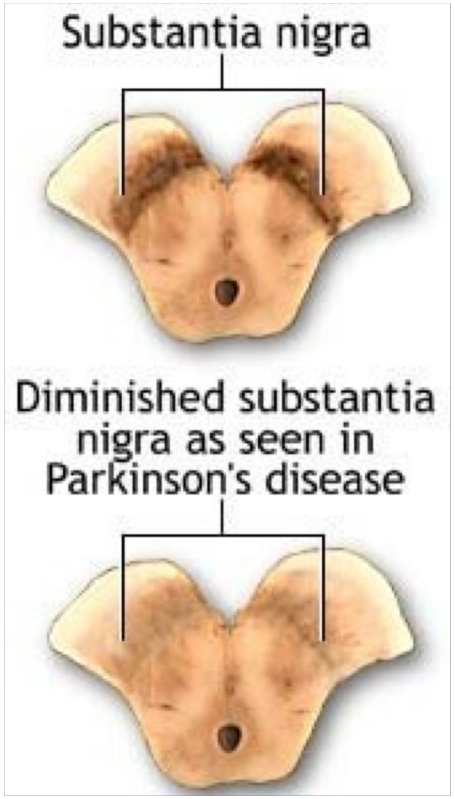
Early Onset PD

Sporadic PD:

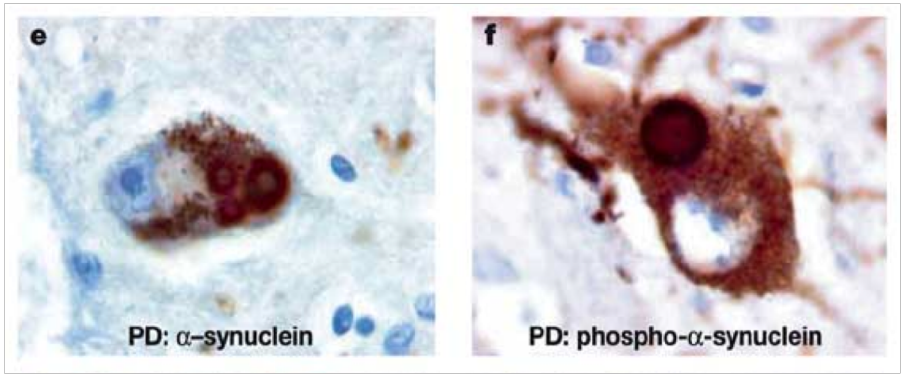
- associated with risk factors, notably **aging (>50 yrs)** and **exposure to pesticides** (*e.g.* **rotenone**) **or herbicides** (*e.g.* **Agent Orange**)

IV. C. Histopathological features of Parkinson's Disease

Macroscopic



Microscopic



Lewy bodies and Lewy neurites *(intracellular aggregates of* ***α-Synuclein*** *in the soma and neurites respectively)*

nature medicine

Ross & Poirier (2004) Nat Med, **10 Suppl**:S10-7.

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VI. D. Symptoms of PD:

The four primary motor symptoms of PD referred as *Parkinsonism* are:

- *tremor* (trembling in hands, arms, legs, jaw, and face)
- *rigidity* (stiffness of the limbs and trunk)
- *bradykinesia* (slowness of movement)
- *postural instability* (impaired balance and coordination).

In the advanced stages of the disease, cognitive and behavioral problems may arise, with dementia commonly occurring (in 30-80% of subjects with PD).

Note:
There is increasing evidence that olfactory dysfunction, sleep abnormalities, cardiac sympathetic denervation, constipation, depression and pain may antedate the onset of motor signs of Parkinson's disease.

IV. C. Treatment of PD

There is currently **no cure but treatments exist to drastically relieve motor symptoms:**

- L-DOPA
- dopamine receptor agonists
- Deep Brain stimulation (DBS)

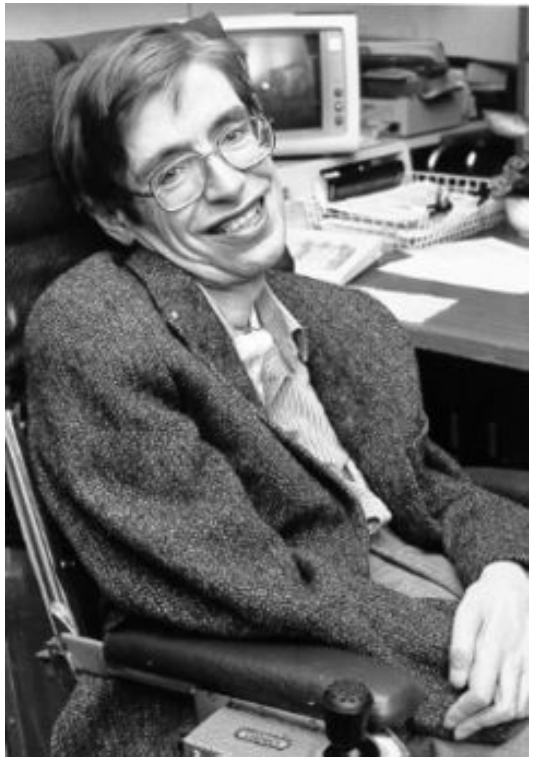
V. Amyotrophic lateral Sclerosis (ALS)

V. A. Definition & classification:

V. A. 1. Definition:

The most common motor neuron disease in human adults is amyotrophic lateral sclerosis (ALS). The primary hallmark of ALS is the **selective killing of motor neurons, which initiates a progressive paralysis in mid-life.**

Lou Gehrig



Stephen Hawking

Stephen Hillenburg

V. B. Classification:

90% Sporadic

Late Onset ALS (~60 yrs)

10% Familial

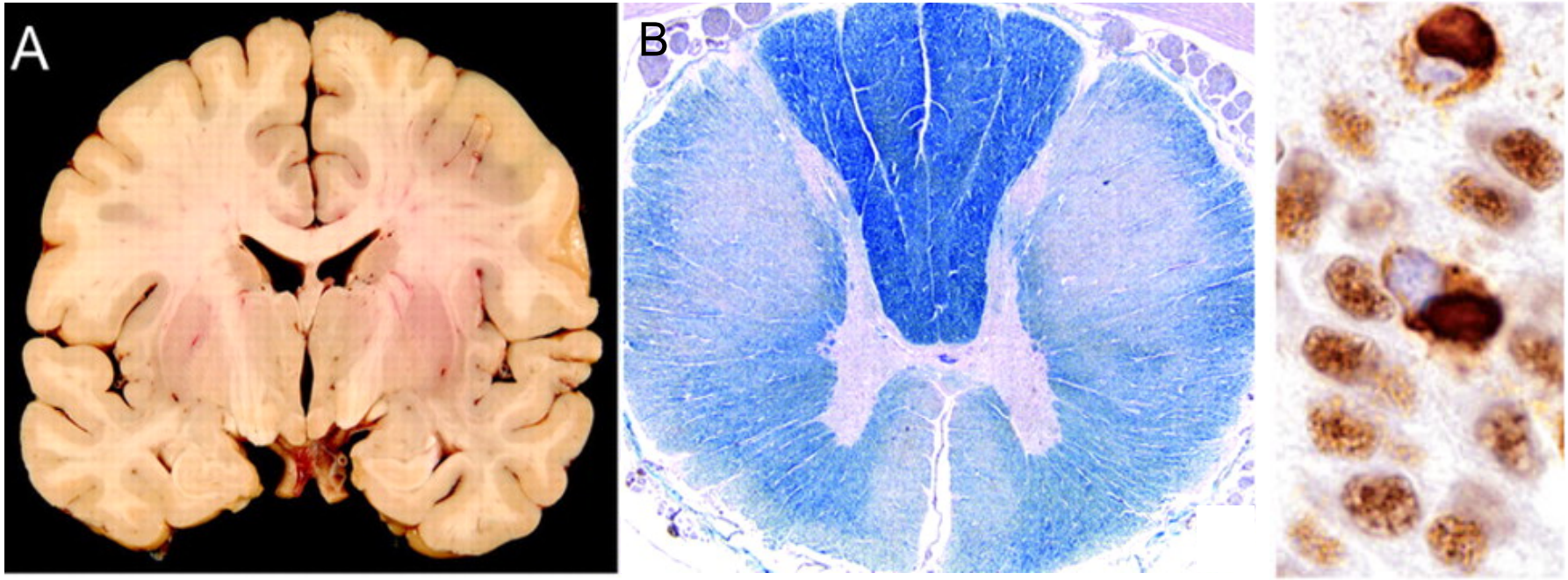
- *C9ORF72 (40-50% fALS)*
- *SOD1 (Cu/Zn Superoxide Dismutase-1) (20% of fALS),*
- *TDP-43 (TAR DNA Binding Protein-43)*
- *FUS (fused in sarcoma)*
- *ATXN2 (ataxin-2)*
- *and ALS2, SETX, VAPB, ANG, FIG4, OPTN, VCP*

Early Onset ALS (~48 yrs)

sALS is associated with risk factors, notably **aging (mean onset at ~55 yrs)** and **gender** (*the male:female ratio is 3:2*)

V. C. Histopathological features of ALS:

Macroscopic	Microscopic



TAR DNA-binding protein 43 (TDP43) was identified in 2006 as the **major constituent of the proteinaceous inclusions** that are characteristic of most forms of ALS and FTLD-TDP.

Parashari et al., 2011 (Int J Nutr Pharm Neurol Dis)
Lee et al. (2012) *Nat Rev Neurosci*; **13**, 38-50
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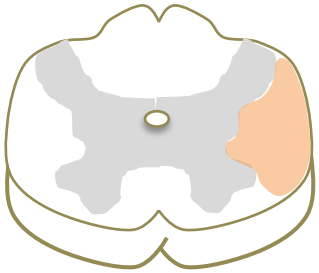
V. D. Symptoms of ALS:

ALS is the most common of the motor neuron diseases (MNDs).

The hallmark of this disease is **the selective death of motor neurons in the brain and spinal cord, leading to paralysis of voluntary muscles.**



ALS is characterized by:

- *progressive weakness and atrophy of muscles,*
- *dysarthria* (difficulty speaking),
- *dysphagia* (difficulty swallowing),
- *decline in breathing ability.*

Usually, sensory neurons are spared.

IV. C. Treatment of ALS

There is currently **no cure but treatment with:**

- **sodium channel blocker**
  Riluzole (Rilutek®)
  modestly increase survival (~up to 12 months)

VI. Neurodegenerative diseases with nucleotide repeat expansions

VI. A. Huntington's disease (HD):

VI. A. 1. Definition:

Huntington's disease (HD) is a **neurodegenerative genetic disorder** that affects **muscle coordination and leads to cognitive decline** and psychiatric problems.

In HD, **medium spiny neurons** of the *striatum* are particularly vulnerable to cell death, and also leads to the dysfunction and death of neurons in other brain regions, including the substantia nigra, cortex, hippocampus, thalamus and cerebellum.

The disease is caused by an *autosomal dominant* mutation in the Huntingtin (*HTT*) gene, which consists in an **expansion of a trinucleotide (CAG) repeat stretch** (polyglutamine or polyQ) within the Huntingtin gene.

VI. A. 2. Clinical classification:

Genetic

- due to “mutations” in *Htt (Huntingtin)*
- Aberrant CAG expansion can reach **250 trinucleotide repeats**
- **Direct relationship between length of the expansion and disease onset**
  (Subjects with >60 CAG will develop a severe juvenile form of HD)

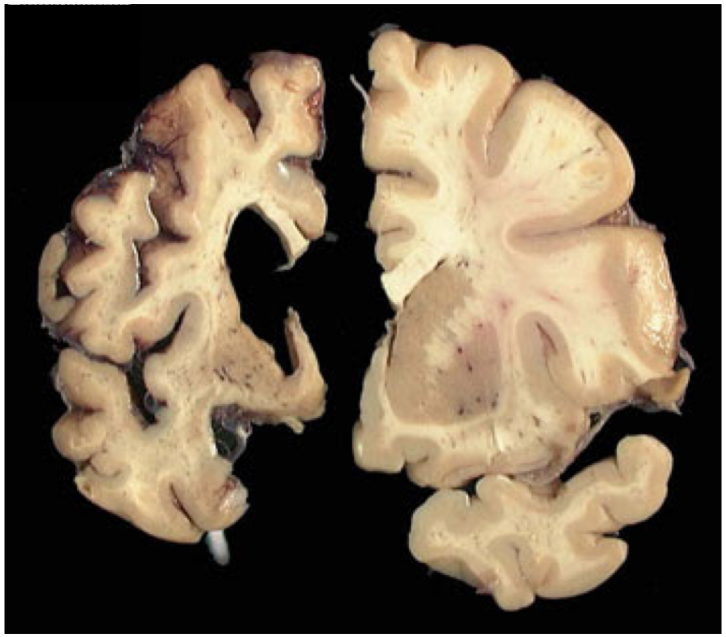
Repeat length	Classification	Disease status
<35	Normal	Unaffected
36-39	Increased Risk	+/-Symptomatic
>40	Full penetrance	Symptomatic

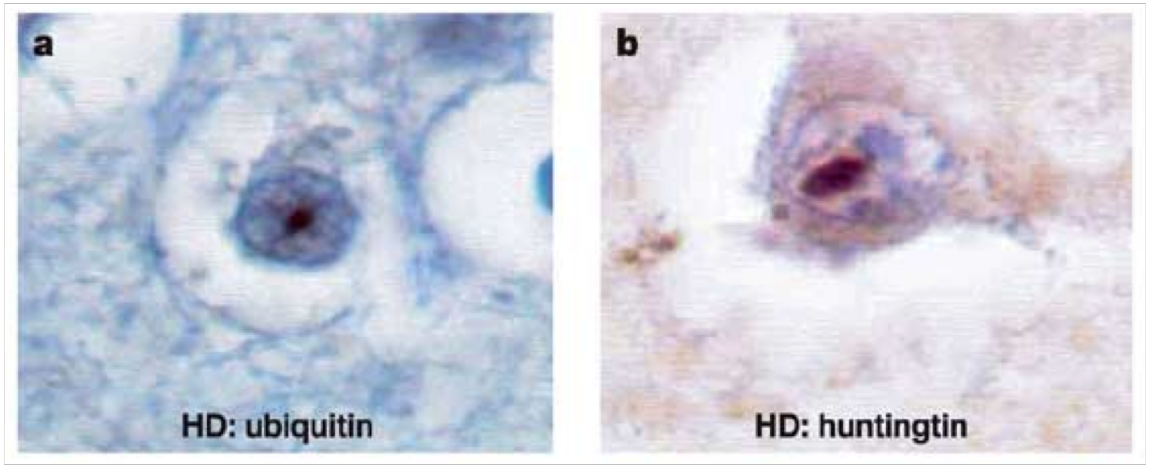
← Pathological threshold

VI. A. 3. Histopathological features of HD:

Huntington's disease is neuropathologically characterized by the appearance of **nuclear and cytoplasmic inclusions** that contain **mutant huntingtin and polyglutamine.**

Macroscopic	Microscopic





nature medicine

Ross & Poirier (2004) Nat Med, **10 Suppl**:S10-7.
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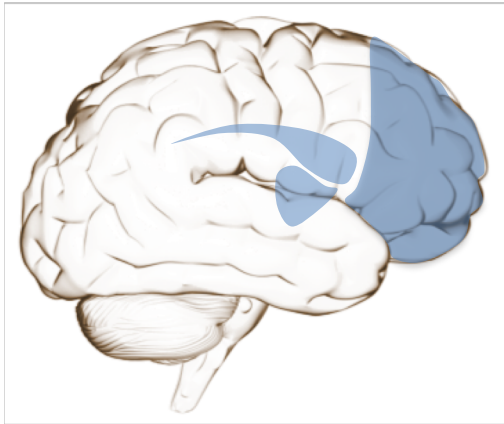
VI. A. 4. Symptoms of HD:



The most characteristic symptoms are:

- *Chorea* (random and uncontrollable movements) (**initial**)
- *rigidity, writhing motions or abnormal posturing* (**with disease progression**)
- *Mood and personality changes*
- *Cognitive decline*

Physical symptoms of HD can start at any age from infancy to old age, but often begin between **35-44 years of age**.

VI. A. 5. Treatment of HD:

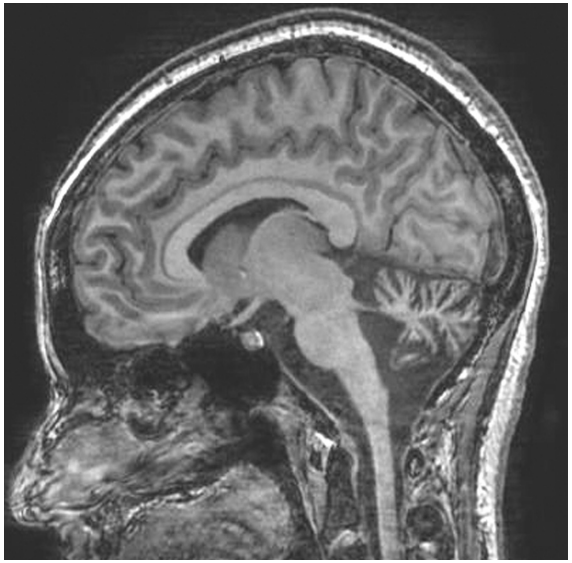
There is currently **no cure but treatments exist to relieve motor and cognitive symptoms:**

- **monoamine transport inhibitors**
  Tetrabenazine
- **Antipsychotics**
  risperidone (Risperdal®)
- **Physical and speech therapy**

VI. B. Other forms of trinucleotide repeat expansion diseases:

Polyglutamine (polyQ) diseases

Type	Gene	Pathogenic repeats
SCA1	ATXN1 (ataxin-1)	49-88
SCA2	ATXN2	33-77
SCA3	ATXN3	55-86
SCA6	CACNA1A (P/Q calcium channel 2.1)	21-30
SCA7	ATXN7	38-120
SCA17	TBP (TATA-binding protein)	47-63
SBMA	AR (androgen receptor)	38-62
DRPLA	ATN1 (atrophin)	49-88



Tazen et al., 2012; *Movement Disorders*

Non-polyglutamine diseases

Type	Gene	Repeat	Pathogenic repeats
FRDA (Friedreich's ataxia)	FXN (frataxin)	GAA	>100
SCA8	SCA8	CTG	110-250
SCA12	SCA12	CAG-5'UTR	66-78

Take 🏡 messages

1- Neurodegenerative diseases are affect different regions of the brain and are fatal

2- The primary determinant of these diseases is aging

3- Neurodegenerative mechanisms poorly understood

4- There are no treatments modifying these diseases