D012512A – Neurogenetics 2023-2024

NEURODEGENERATIVE BRAIN DISORDERS

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CENTRUM MEDISCHE GENETICA GENT

OUTLINE

- Introduction
- Alzheimer’s disease
- Related disorders: frontotemporal dementia –ALS spectrum

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OUTLINE

- **Introduction**
- Alzheimer’s disease
- Related disorders: frontotemporal dementia –ALS spectrum

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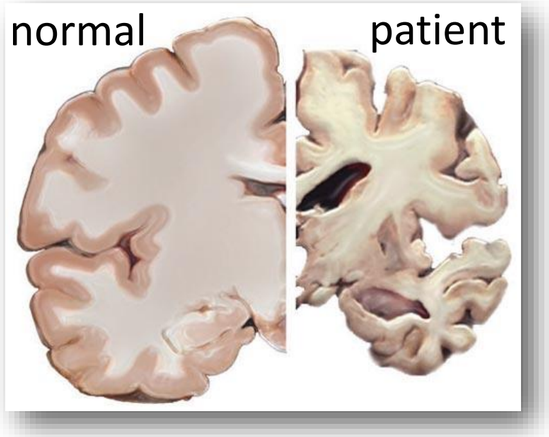
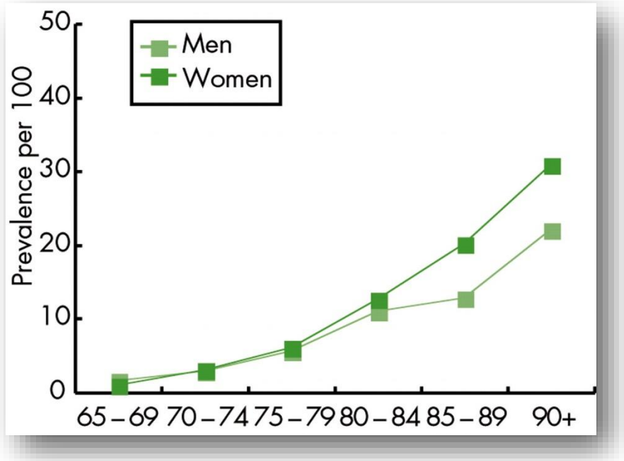
NEURODEGENERATIVE BRAIN DISORDERS





✓**progressive** loss of neurons, neuronal function

✓ **many subtypes**:

- frequent: Alzheimer (60-70%), frontotemporal dementia (<5%), Parkinson (10%)
- rare: prion disorders, motor neuron disease, Huntington's disease, …

✓**societal problem** is huge:

- Aging population – 65+ :
  - ➢16% (2015) → 25% (2030)
- dementia:
  - ➢ 44 million (2014) → 66 million (2030)

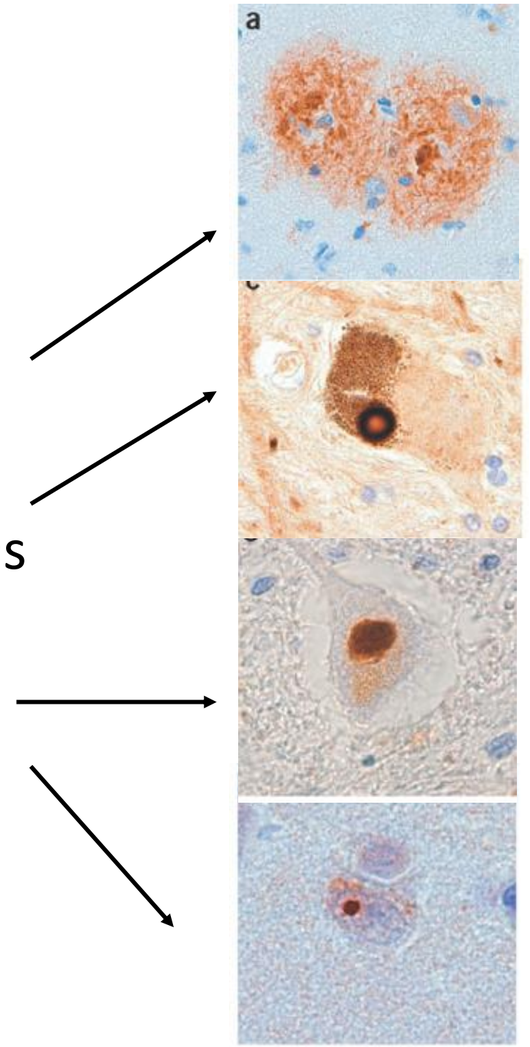
✓**limited therapeutic options**

✓**genetically heterogeneous**

NEURODEGENERATIVE BRAIN DISORDERS

- Chronic and progressive disorders
- Progressive and selective loss of neurons
  Motor, sensorial and cognitive system
- Nosological classification following pattern of neuronal loss and **disease-specific cellular markers**
  “Proteinopathies”

AD:	senile plaques, neurofibrillary ‘tangles’ neuronal loss
PD:	Lewy bodies, depletion of dopaminergic neurons
ALS:	cellular inclusions, axon swelling of motor neurons
HD:	nuclear inclusions, loss of striatal neurons



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Martin J.B., NEJM 340:1970-1980 (1999)

NEURODEGENERATIVE BRAIN DISORDERS

- Causes
  - Genetic factors

    -**Mendelian** inheritance – monogenic:

    rare familial forms of common disorders

    classic monogenic e.g. repeat expansion disorder

    -**Multifactorial** - common disorders:

    several genes contribute to disease

    variation in age of onset and progression point to different pathogenetic mechanisms (e.g. AD)

  - Environment: ?, toxic or metabolic processes, infection, unknown

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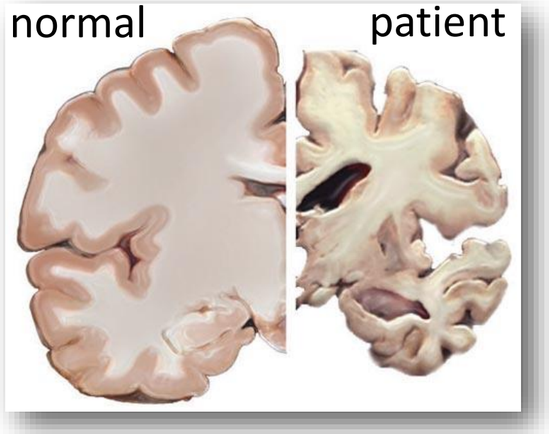
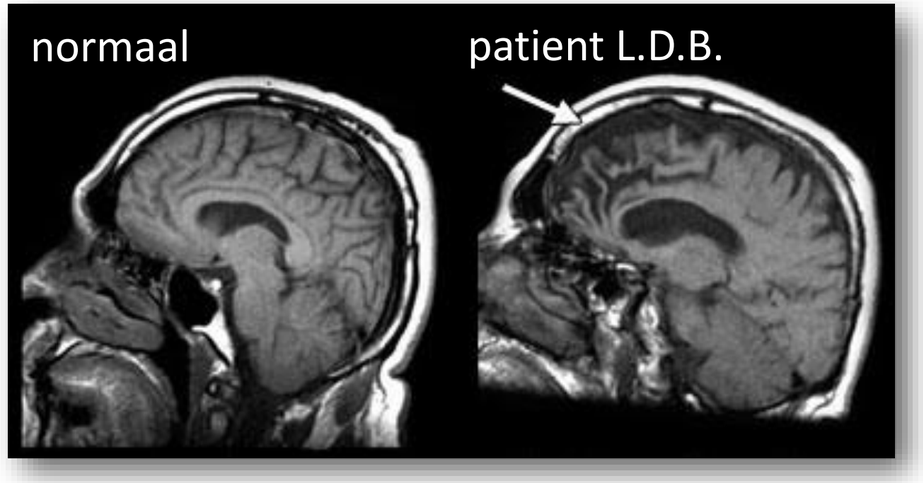
PATIENT L.D.B.



- ✓ male, 56 years, negative neuropsychiatric history
- ✓ admitted to emergency psychiatric service after car accident:
  - restless, incoherent thinking, stereotypical vocabulary, word finding problems
  - known to the police: shoplifting, aggressiveness, dangerous driving behavior
- ✓ According to brother: last 3 yrs increasing compulsive behavior, conflicts, emotional flattening, contentless speech, memory problems
- ✓ Brain imaging: atrophy of the frontal and temporal lobes
- ✓ **mother, maternal grantfather both demented < 65 yrs**



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→ diagnosis **early-onset dementia: subtype?**

EARLY-ONSET DEMENTIA

- ✓ “early-onset” dementia : age of onset **< 65 years**

- ✓ “late-onset” age of onset after 65 jaar:
  - ✓ >90% Alzheimer’s disease
  - ✓ Vascular dementia

- ✓ “early-onset dementia:
  - ✓ **Alzheimer**’s disease
  - ✓ **frontotemporal** dementia

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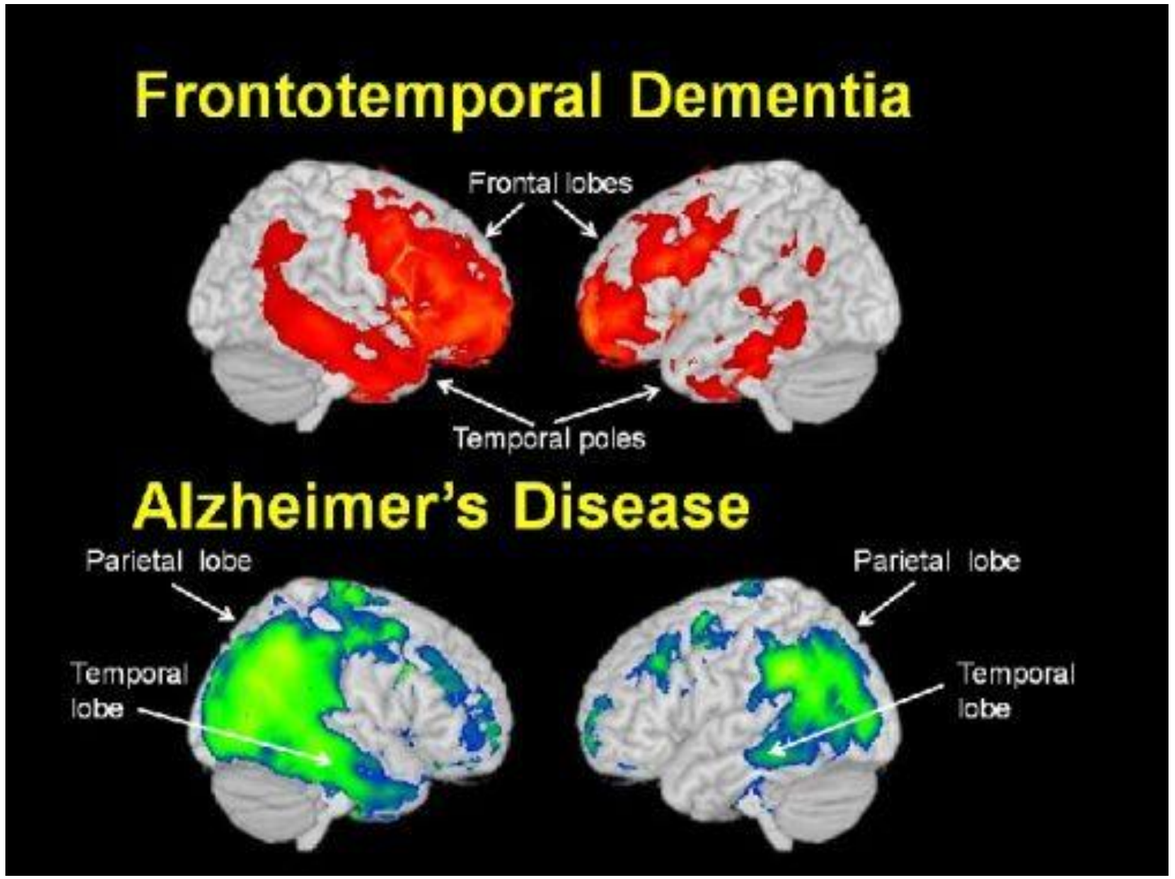
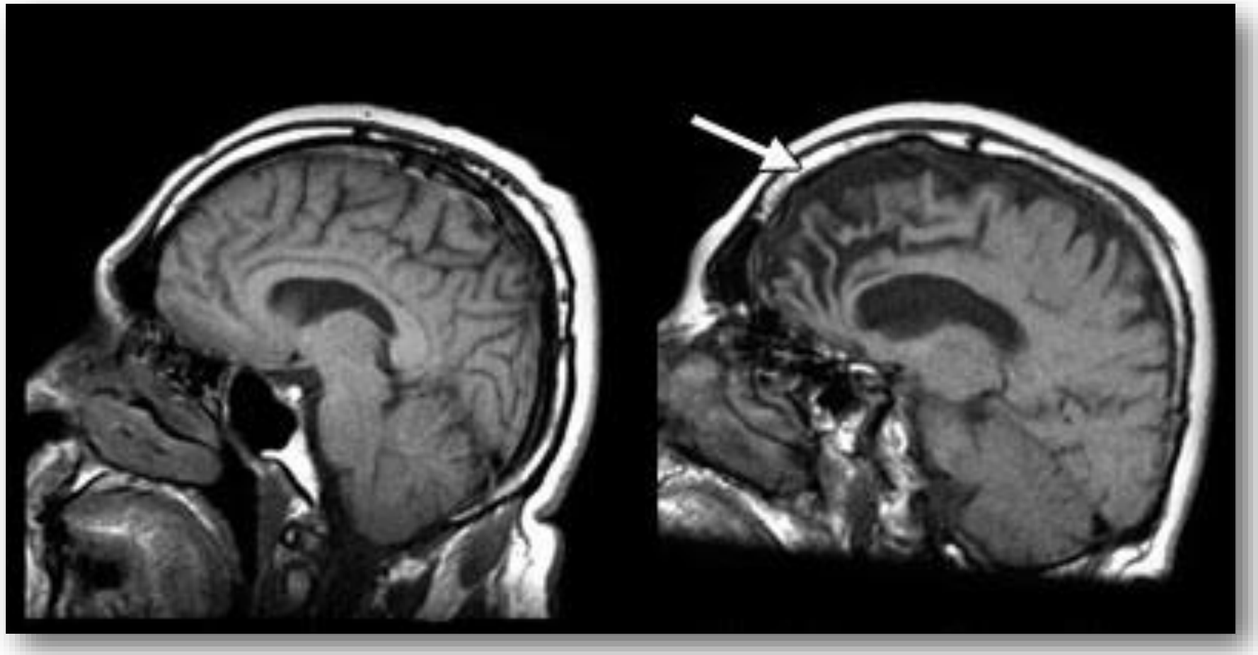
ALZHEIMER VS. FRONTOTEMPORALE DEMENTIA





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ALZHEIMER VS. FRONTOTEMPORALE DEMENTIE

Table 2. Relative Frequency of Features of Frontotemporal Dementias and Alzheimer Disease

	Relative frequency of syndrome features					
Syndrome	*Behavioral or personality changes*	*Loss of object knowledge and comprehension deficits*	*Nonfluent speech output, agrammatism, telegraphic speech*	*Extrapyramidal features*	*Psychosis*	*Memory loss*
Frontotemporal dementia						
Behavioral variant	✓✓✓	✓	✓	✓	✓	✓
Semantic	✓✓*	✓✓✓	✓	✓	✓	✓
Progressive nonfluent aphasia	✓	✓✓	✓✓✓	✓✓†	✓	✓✓
Alzheimer disease	✓	✓	✓	✓	✓✓	✓✓✓

*—Distinct from behavioral variant frontotemporal dementia.
†—Occurs late in disease.

→ diagnosis **early-onset dementia pt L.D.B.: suspicious for FTD**

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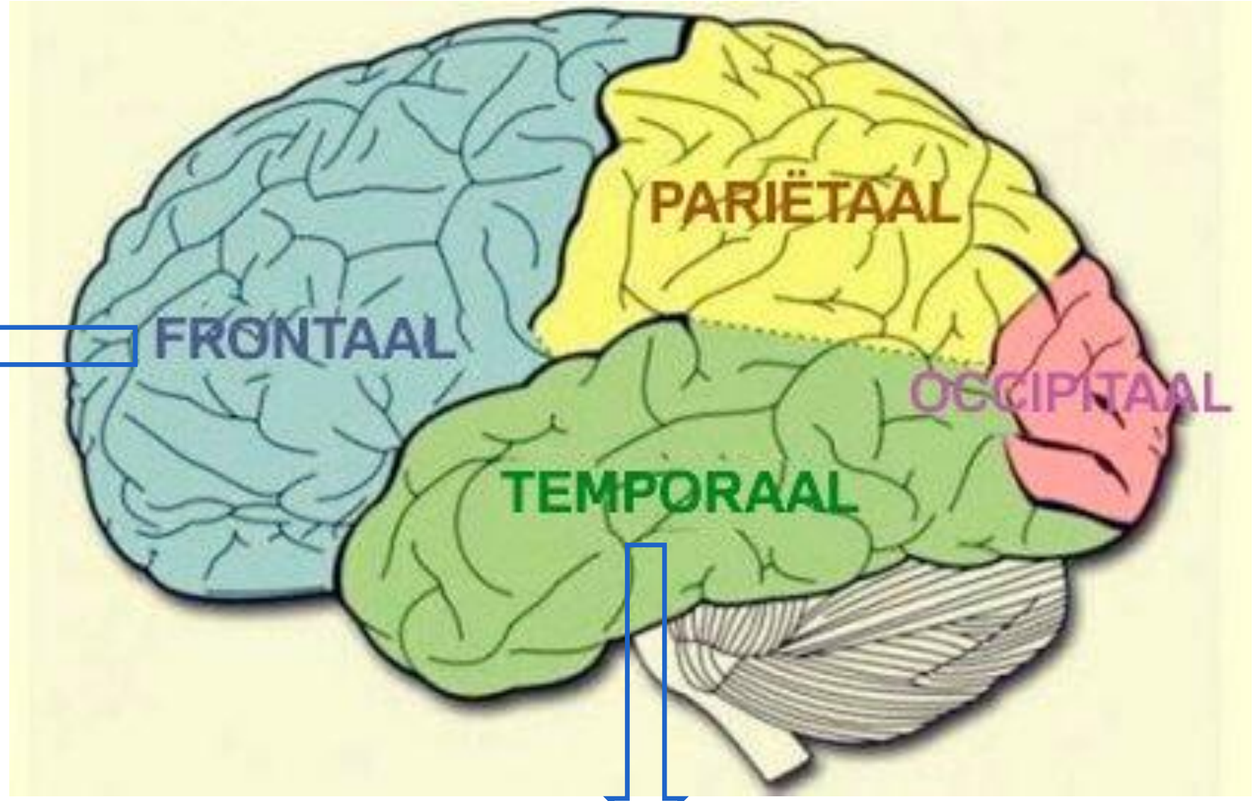
FRONTOTEMPORAL DEMENTIA

behaviour



language/speech

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FRONTOTEMPORAL DEMENTIA

- ✓ **Signs from relatives/close friends/colleagues:**
  - ✓ lack of disease insight by patient
  - ✓ partner is worried about the behaviour of the patiënt, relational problems
  - ✓ stress, burn-out, concentration problems, depression (most common initial diagnoses)

FRONTOTEMPORAL DEMENTIA

- ✓ **Other signs**:

  - ✓ Clear change in personality
  - ✓ Inadequate behaviour
  - ✓ Poor job performance
  - ✓ Emotional instability
  - ✓ Mood swings
  - ✓ Relational problems
  - ✓ Fatigue
  - ✓ Paranoia
  - ✓ Obsessive-compulsive behaviour
  - ✓ Apathy
  - ✓ Lack of empathy
  - ✓ (verbal) agression
  - ✓ Hypo- or hypersexual behaviour
  - ✓ Egocentric behaviour
  - ✓ Alcoholism

FRONTOTEMPORAL DEMENTIA

- ✓ After Alzheimer second most common form of early-onset dementia
- ✓ Prevalence**:** < 65 years **4-15/100.000**, general practitioner: ~ one FTD patient in her/his practice.
- ✓ Onset mostly between 40-60 years, peak between **50 and 60 years**.
- ✓ 25% FTD = inherited, autosomal dominant.

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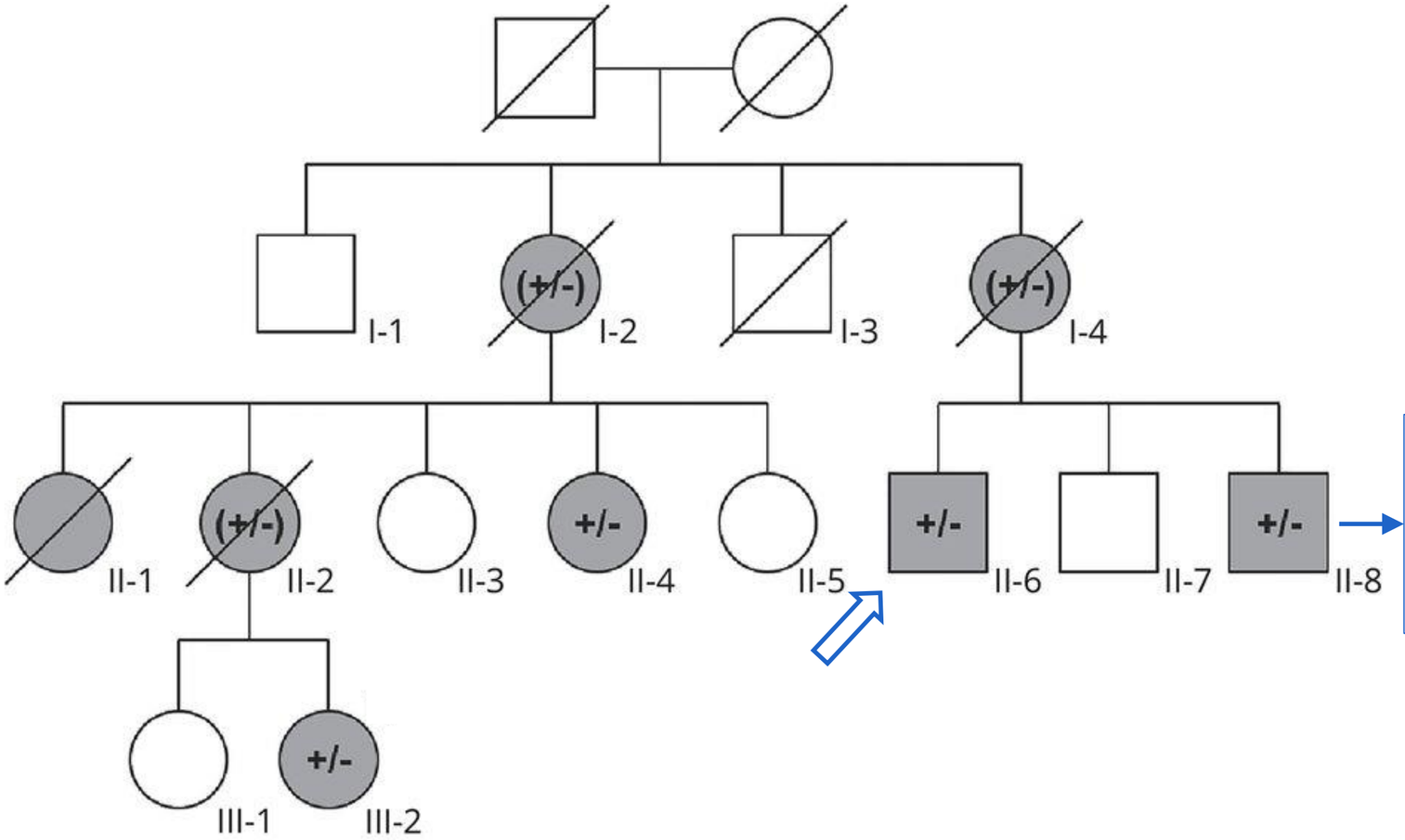
PATIËNT L.D.B. – FAMILY HISTORY



depression, slow, stuttering speech, onset 49 yrs

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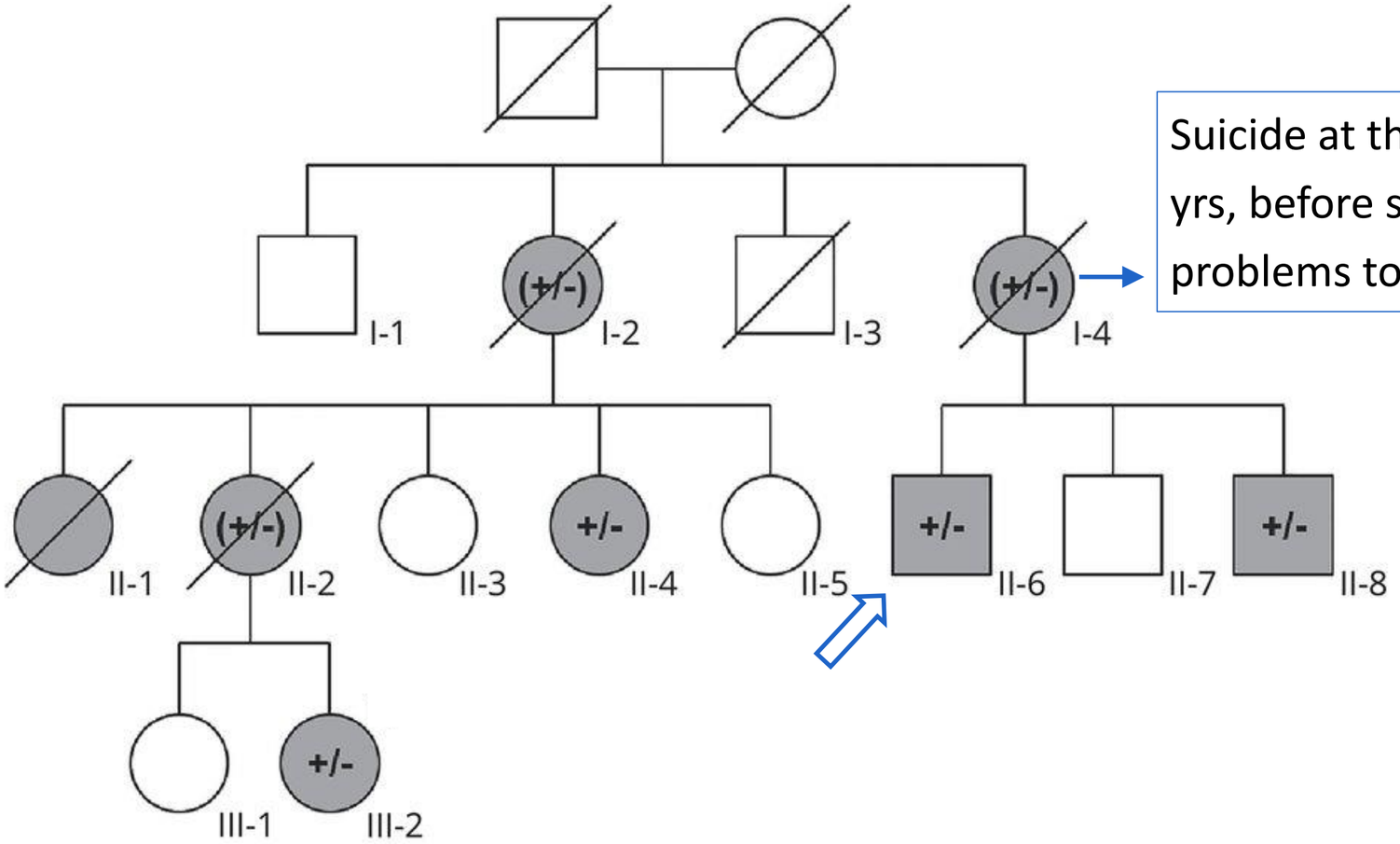
PATIËNT L.D.B. – FAMILY HISTORY



Suicide at the age of 52 yrs, before severe problems to manage shop

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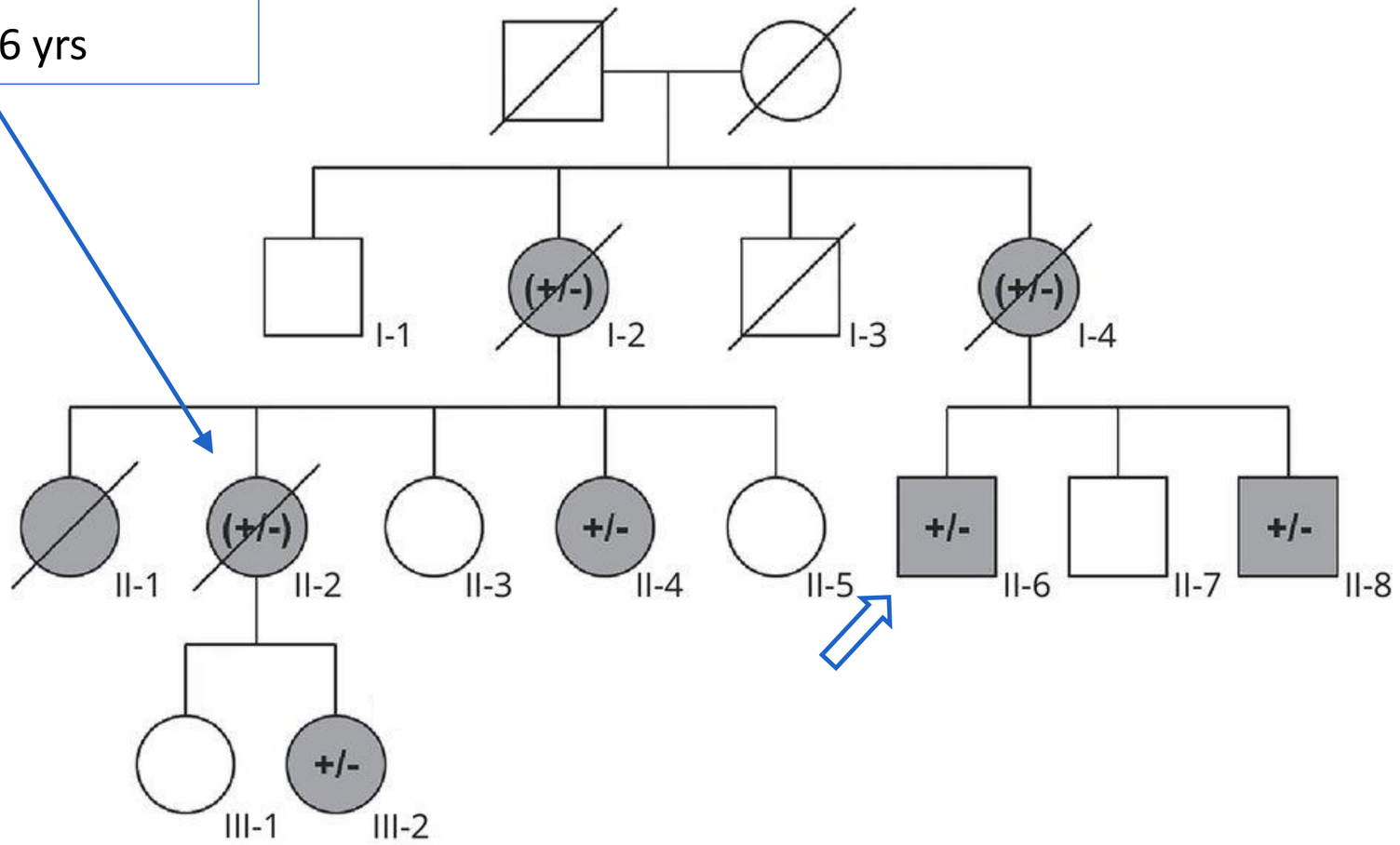
PATIËNT L.D.B. – FAMILY HISTORY

diagnosis FTD at 47 yrs,
deceased at 56 yrs



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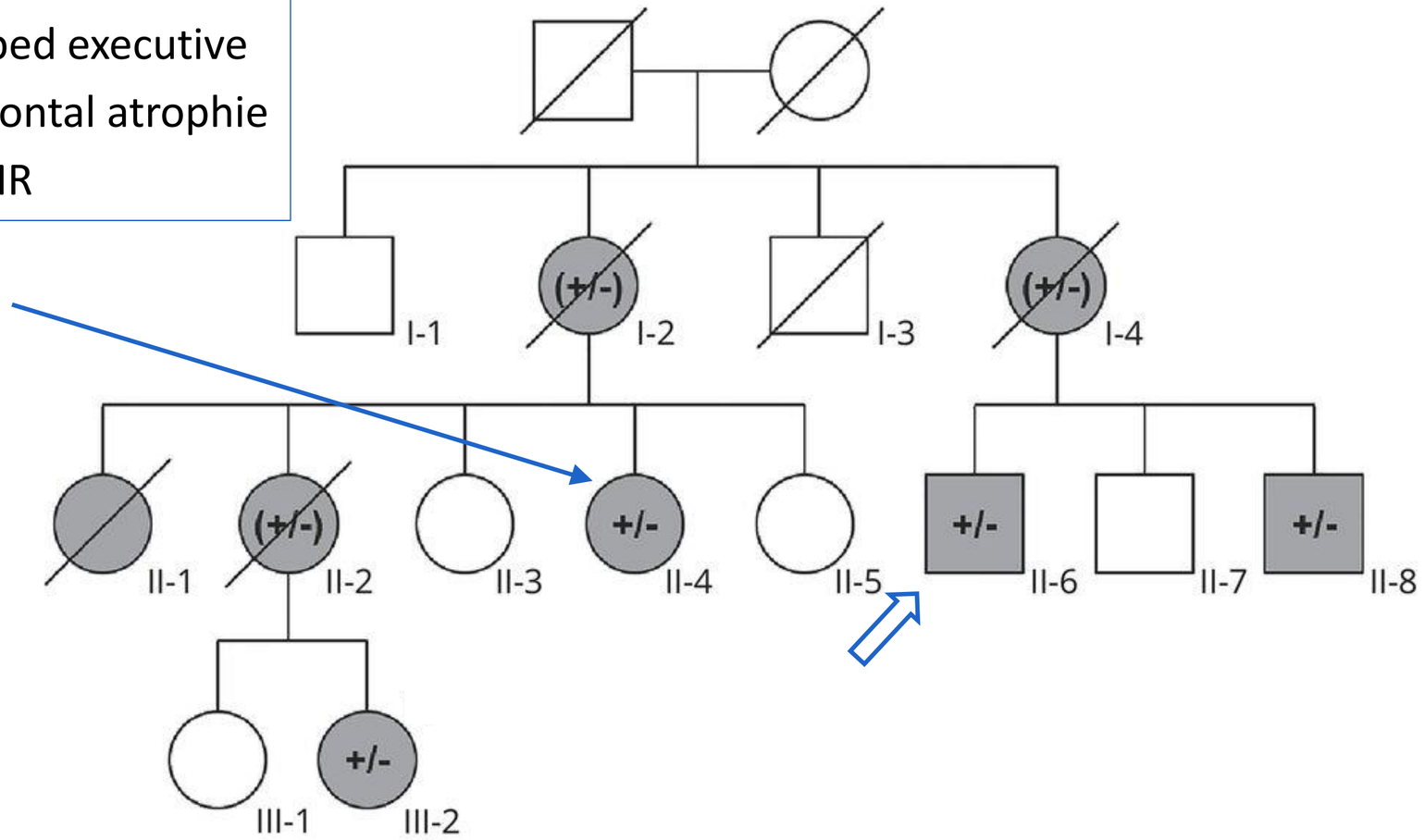
PATIËNT L.D.B. – FAMILY HISTORY

60 years, depression, slow, disturbed executive functions, frontal atrophie on brain NMR



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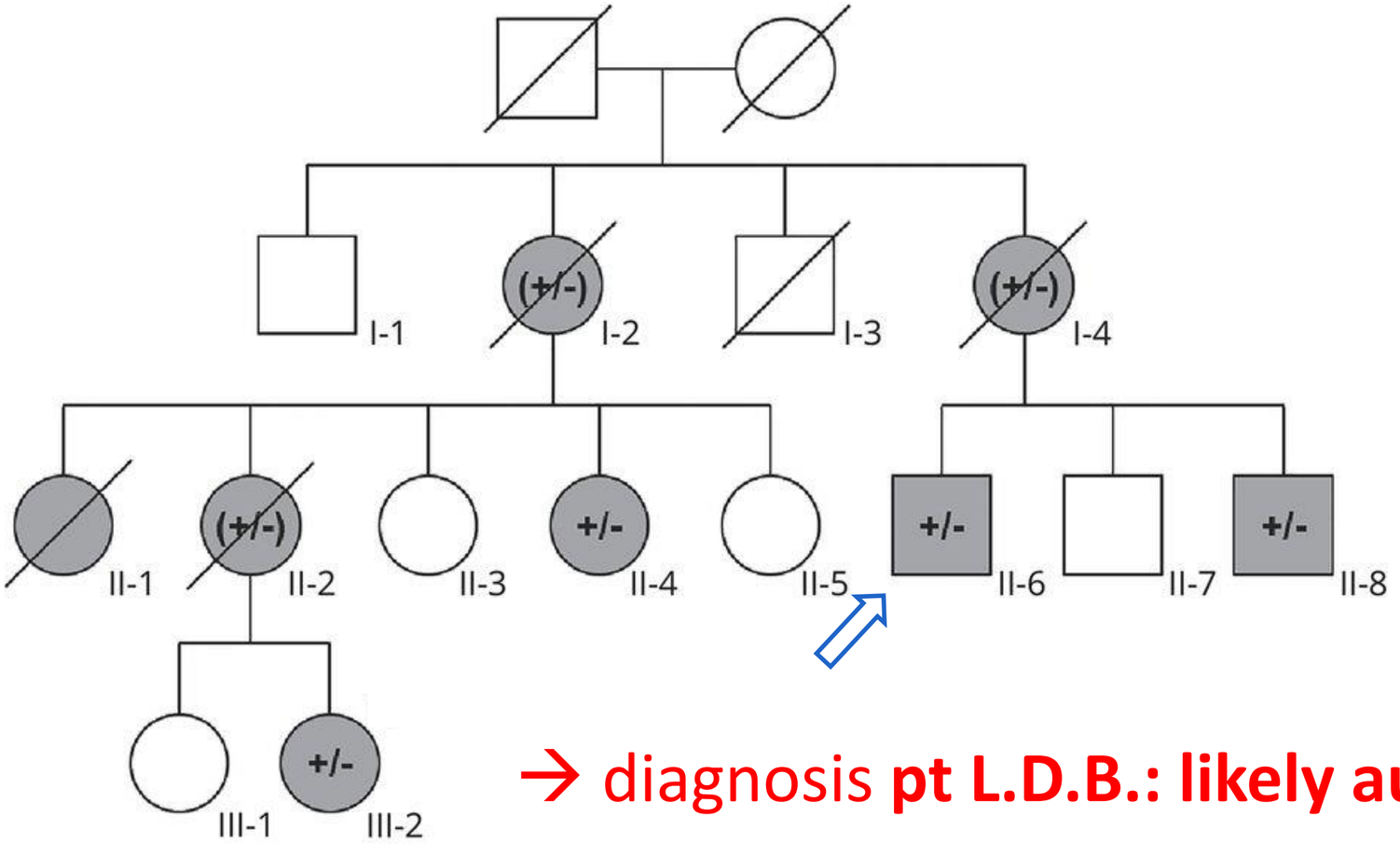
PATIËNT L.D.B. – FAMILY HISTORY



→ diagnosis **pt L.D.B.: likely autosomal dominant of early-onset dementia (FTD?)**

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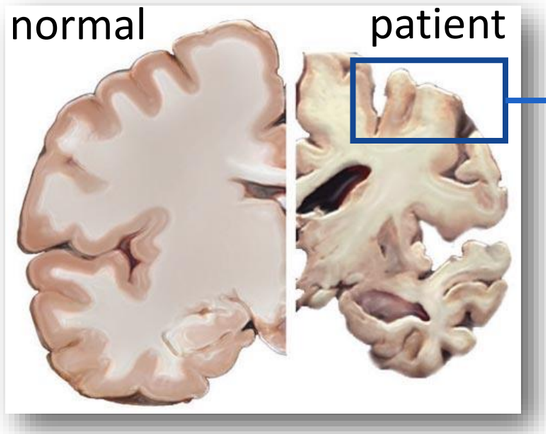
UNDER THE MICROSCOPE…



neuropathologist

Frontotemporal dementia or Alzheimer ?

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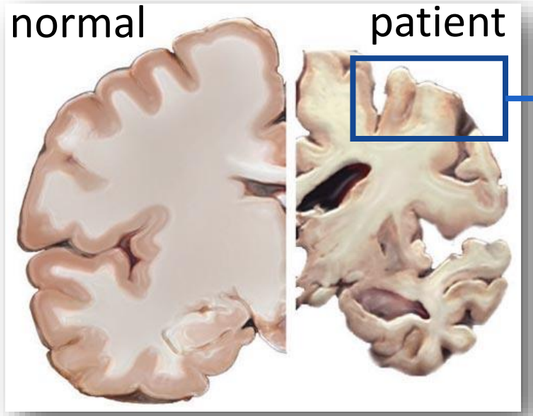
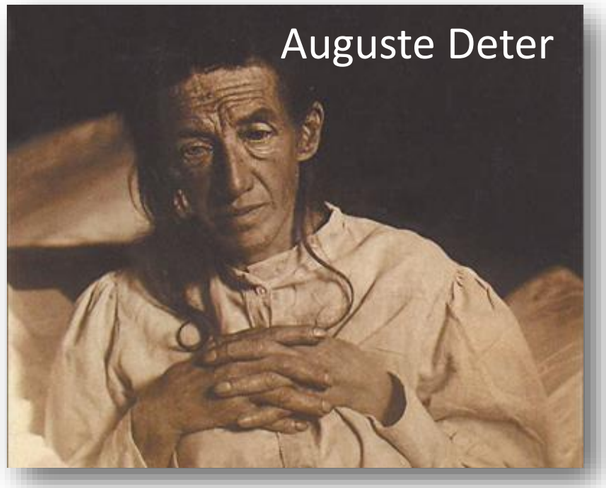


Alzheimer's disease

Amyloid plaques AND **Tau tangles**

Aloïs Alzheimer
(1864-1915)



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Alzheimer A. **Über eine eigenartige Erkrankung der Hirnrinde.** *Allgemeine Zeitschrift für Psychiatrie und Psychisch-gerichtliche Medizin*. 1907 Jan ; 64:146-8.

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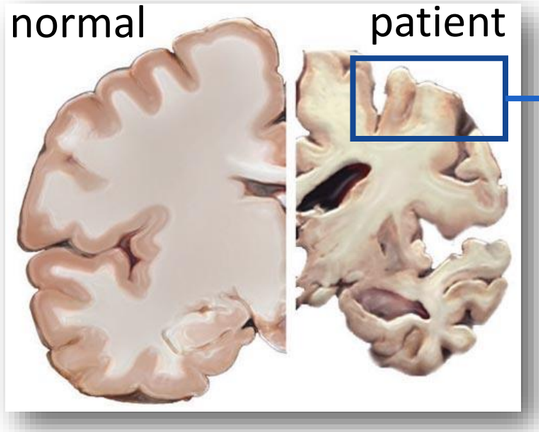


Aloïs Alzheimer (1864-1915)

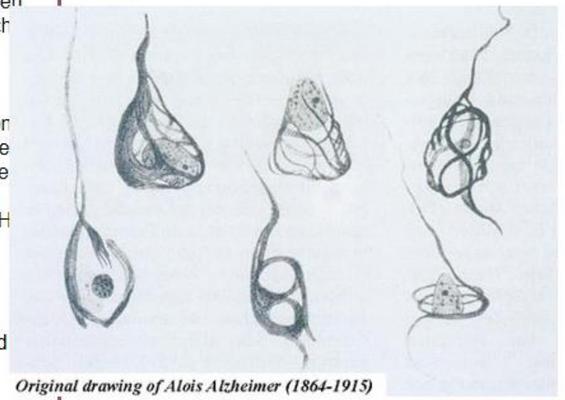
Alzheimer A.
Über eine eigenartige Erkrankung der Hirnrinde
Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin.
1907 Jan ; 64:146-8.

"Die Sektion ergab ein gleichmäßig atrophisches Gehirn ohne makroskopische Herde. Die größeren Hirngefäße sind arteriosklerotisch verändert.
An Präparaten. die mit der Bielschowskyschen Silbermethode angefertigt sind, zeigen sich sehr merkwürdige Veränderungen der Neurofibrillen. Im Innern einer im übrigen noch normal erscheinenden Zelle treten zunächst eine oder einige Fibrillen durch ihre besondere Dicke und besondere Imprägnierbarkeit stark hervor. Im weiteren Verlauf zeigen sich dann viele nebeneinander verlaufende Fibrillen in der gleichen Weise verändert. Dann legen sie sich zu dichten Bündeln zusammen und treten allmählich an die Oberfläche der Zelle. Schließlich zerfällt der Kern und die Zelle, und nur ein aufgeknäueltes Bündel von Fibrillen zeigt den Ort, an dem früher Ganglienzelle gelegen hat.
Da sich diese Fibrillen mit anderen Farbs[illegible]lassen normale Neurofibrillen, muß eine che[illegible]ndung de Fibrillensubstanz stattgefunden h[illegible]ürfte wohl die Ursache sein, daß die Fibrille[illegible]ng der Zelle uberdauern. Die Umwand[illegible]en scheint Hand in H zu gehen mit der Einlageru[illegible]noch nicht näher erforschten pathologischen S[illegible]wechselproduktes in die Ganglienzelle. Etwa 1/4 bis 1/3 aller Ganglienzellen der Hirnrinde zeigt solche Veränderungen. Zahlreiche Ganglienzellen, besonders in den oberen Zellschichten. sind ganz verschwunden."

"Über die ganze Rinde zers[illegible]ers zahlreich in den oberen[illegible]det man miliare Herdch[illegible]ch Einlagerung ein[illegible]n Stoffes in die Hirnrinde[illegible]. Er läßt sich schon ob[illegible]rkennen. ist aber Färb[illegible]aber sehr refractär."

Amyloid plaques

Tau tangles



Original drawing of Alois Alzheimer (1864-1915)

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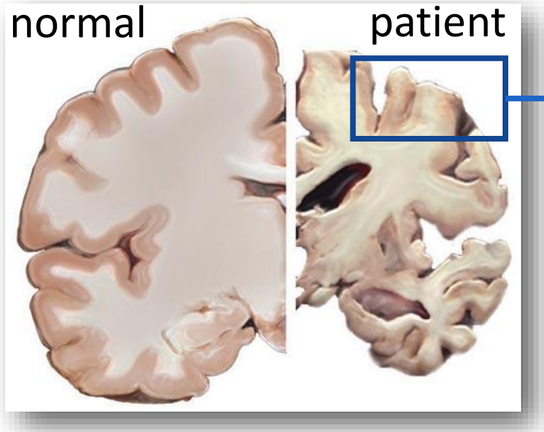
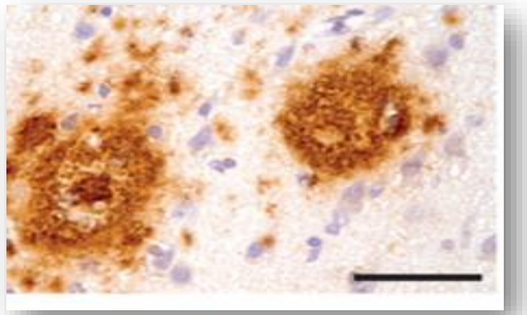
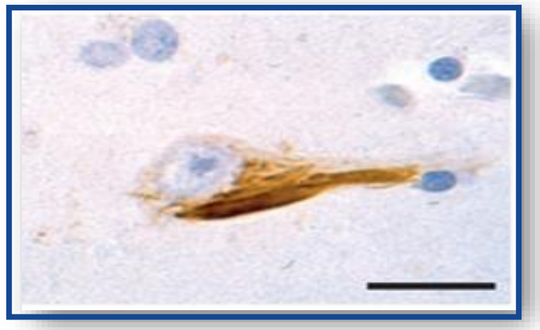


Frontotemporal dementia

Amyloid plaques



Tau tangles



Arnold Pick
(1851-1924)

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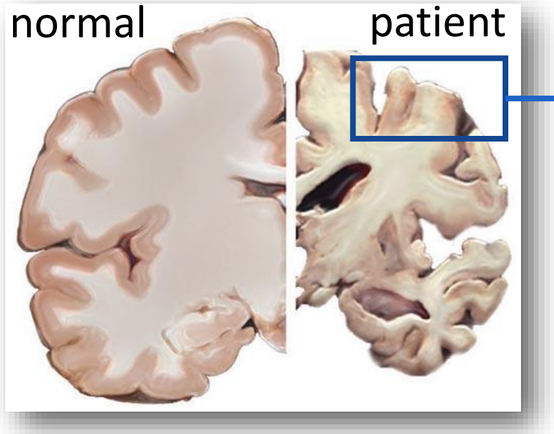
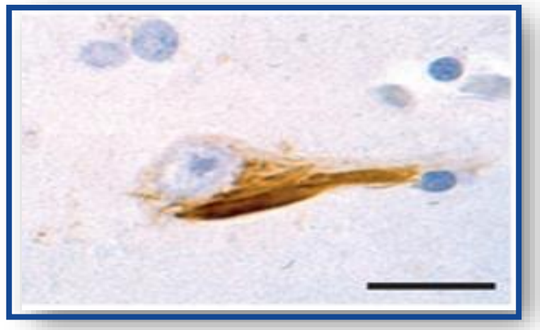


Frontotemporal dementia

Tau tangles



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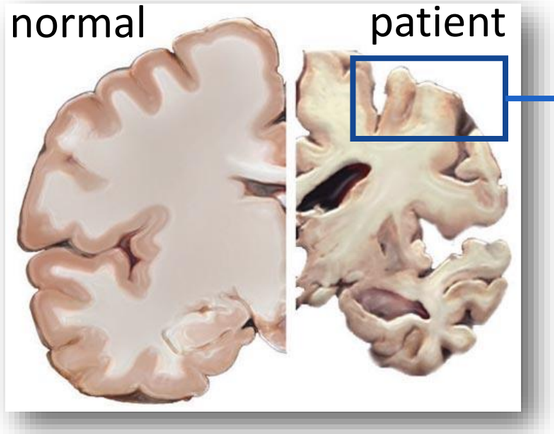
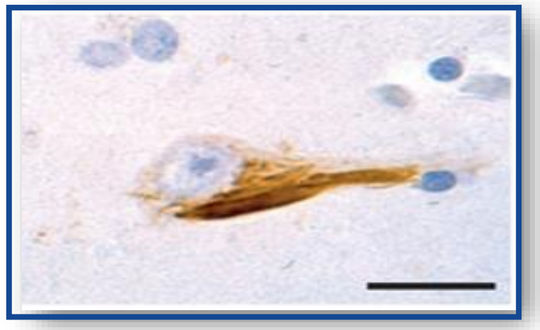


Frontotemporal dementia

Tau tangles



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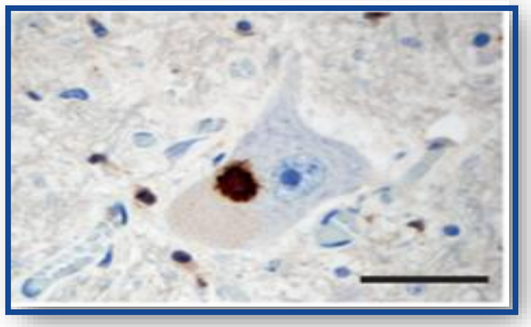

TDP-43 inclusions

Arnold Pick
(1851-1924)

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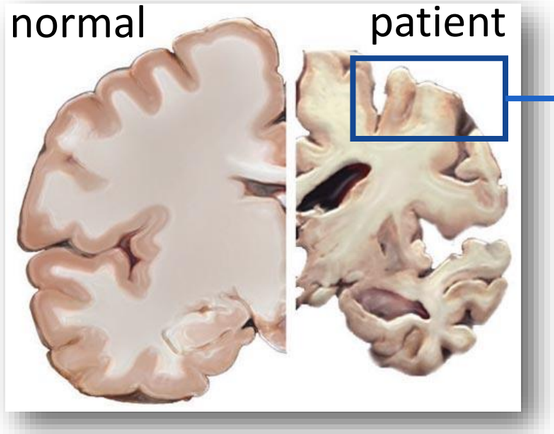
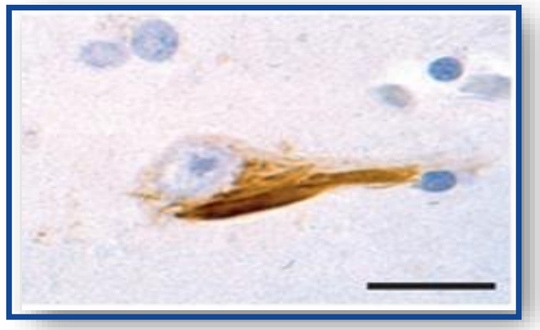


Frontotemporal dementia

Patient L.D.B.

Tau tangles



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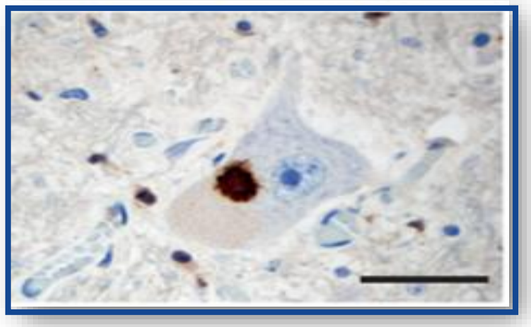
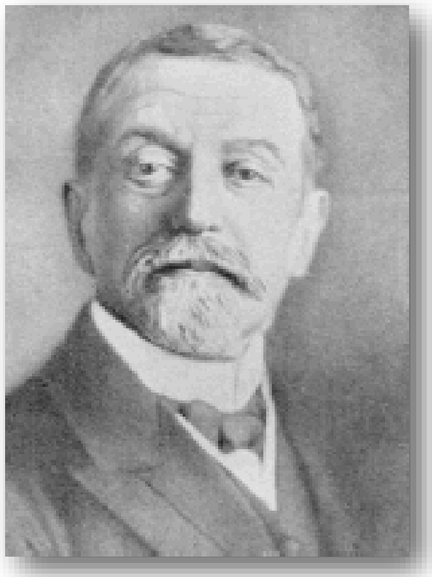


TDP-43 inclusions



Arnold Pick
(1851-1924)

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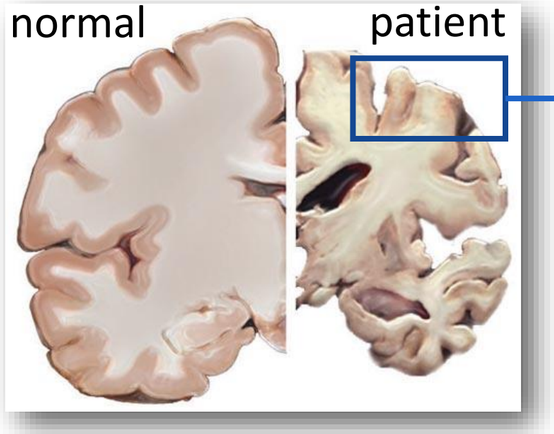
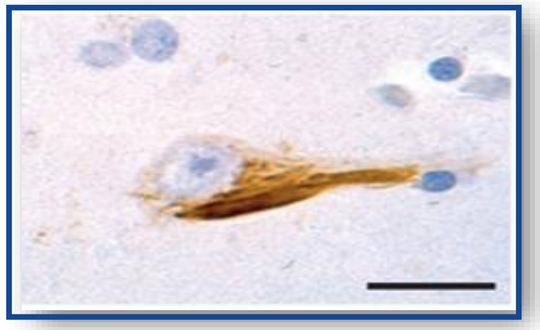


Frontotemporal dementia

Patient L.D.B.

Tau tangles



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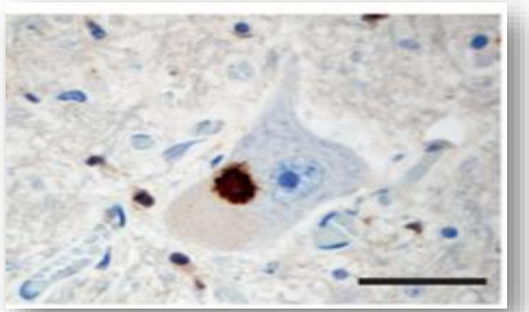
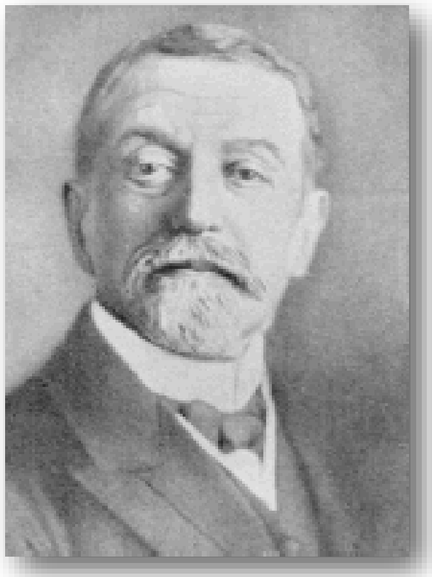


TDP-43 inclusions



Arnold Pick
(1851-1924)

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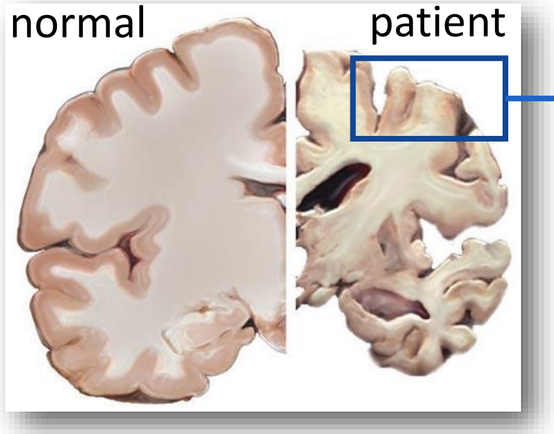
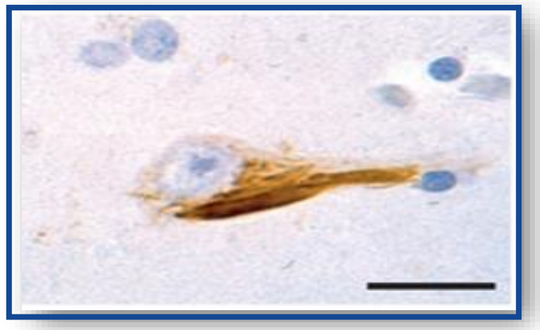
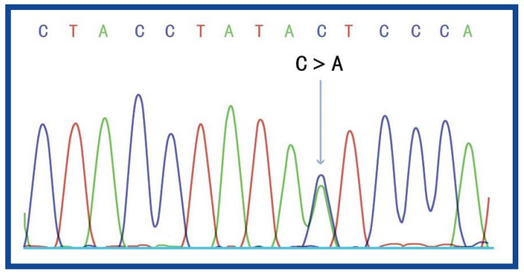


Frontotemporal dementia

Tau tangles



Patient L.D.B.



Arnold Pick
(1851-1924)

defect in the Tau gene (*MAPT* p.P301L)

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→ **Tau-positive familial Frontotemporal dementia**

OUTLINE

- Introduction
- **Alzheimer's disease**
- Related disorders: frontotemporal dementia –ALS spectrum

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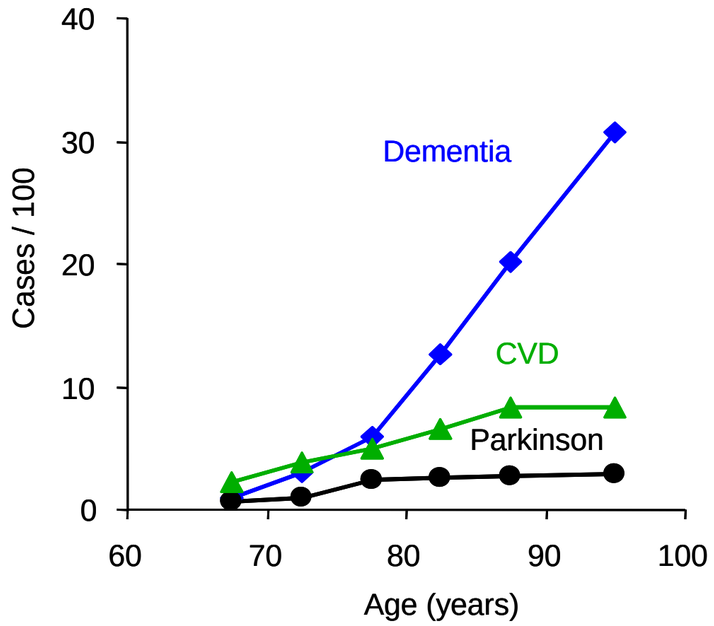
ALZHEIMER'S DISEASE

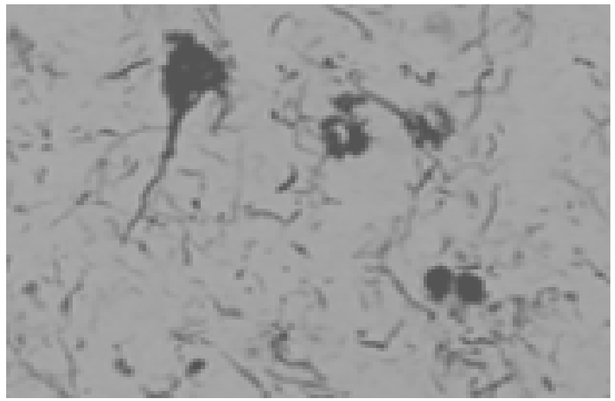
Prevalence strongly increases with age

70% are Alzheimer's disease cases
(860,000 cases in France in 2005)



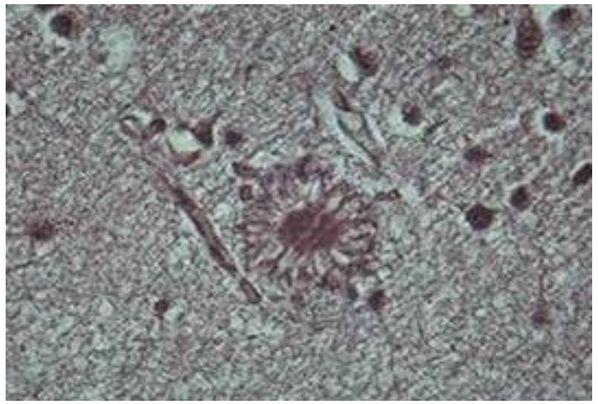
Alzheimer's disease (AD) => characterized in the brain by :

Neurofibrillary degeneration



Intraneuronal accumulation of hyperphosphorylated Tau

Amyloid deposition

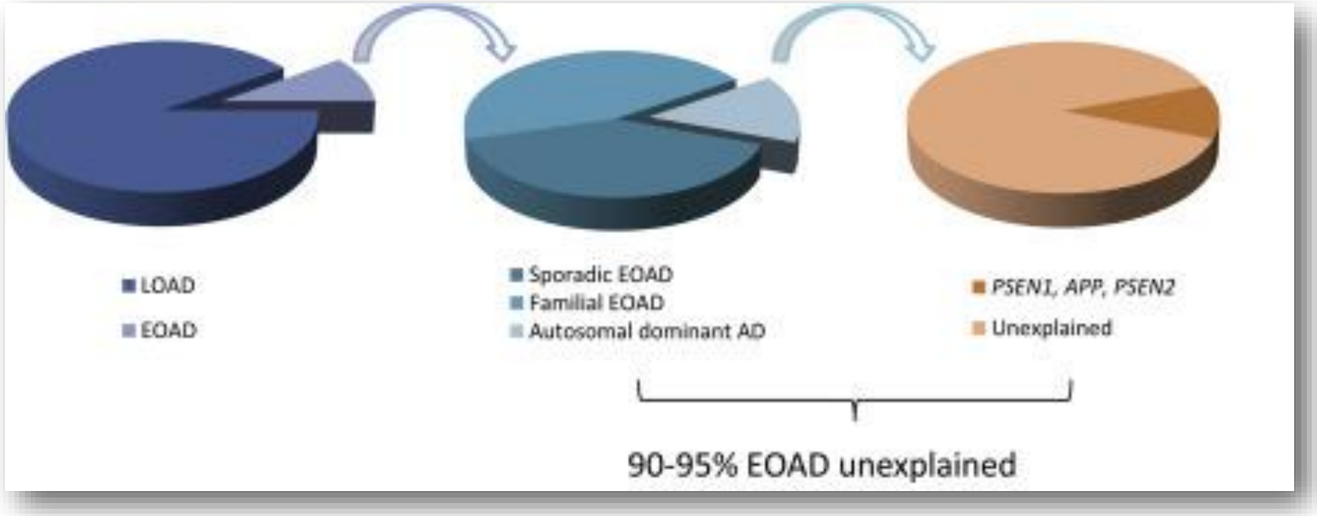


Extracellular accumulation of amyloid peptides

ALZHEIMER'S DISEASE

Disease characteristics

- adult-onset slowly progressive dementia (memory, cognition, personality)
- most frequent form of dementia
- >60 y: 5-10%, >85 y: 45%
- 4 mill/y, 100.000 +/y in US, cost 60 miljard US dollar
- 25% of cases familial
  - mostly late onset
  - < 2% early-onset familial AD (EOFAD)
    symptoms typically < 65 y



Cacace et al, 2016

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ALZHEIMER'S DISEASE

Clinical features

- dementia, typically begins with subtle and poorly recognized failure of memory

- other common symptoms: anxiety, confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations

- occasional symptoms: seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, mutism

- death usually results from general inanition, malnutrition, pneumonia

- typical clinical duration of the disease: 8-10 yrs, range: 1- 25 yrs

- post mortem: macroscopic - microscopic

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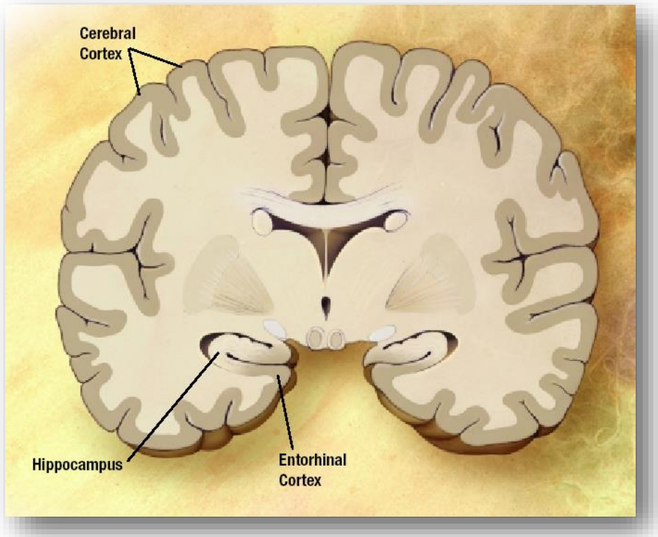
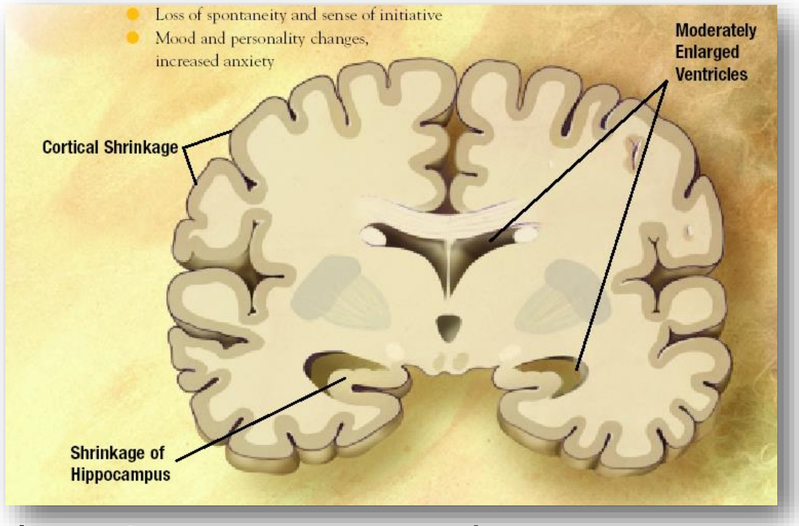
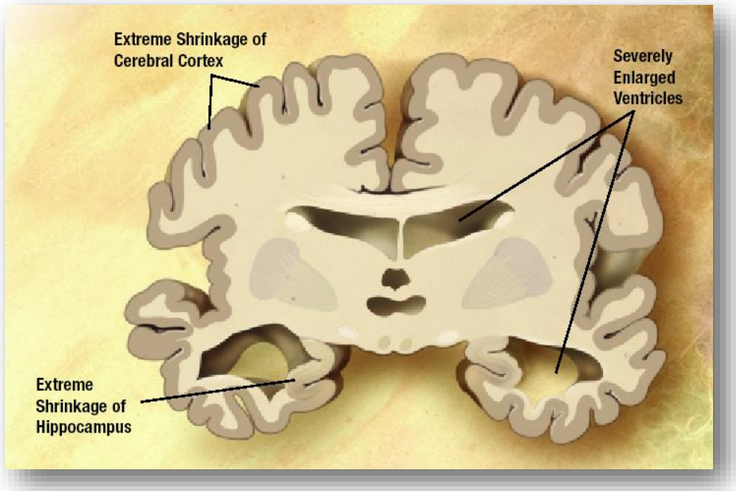
ALZHEIMER'S DISEASE



near and connected to hippocampus



learning processes, short term memory and conversion to long term memory in other parts (olfactory bulb, amygdala, nucleus basalis)



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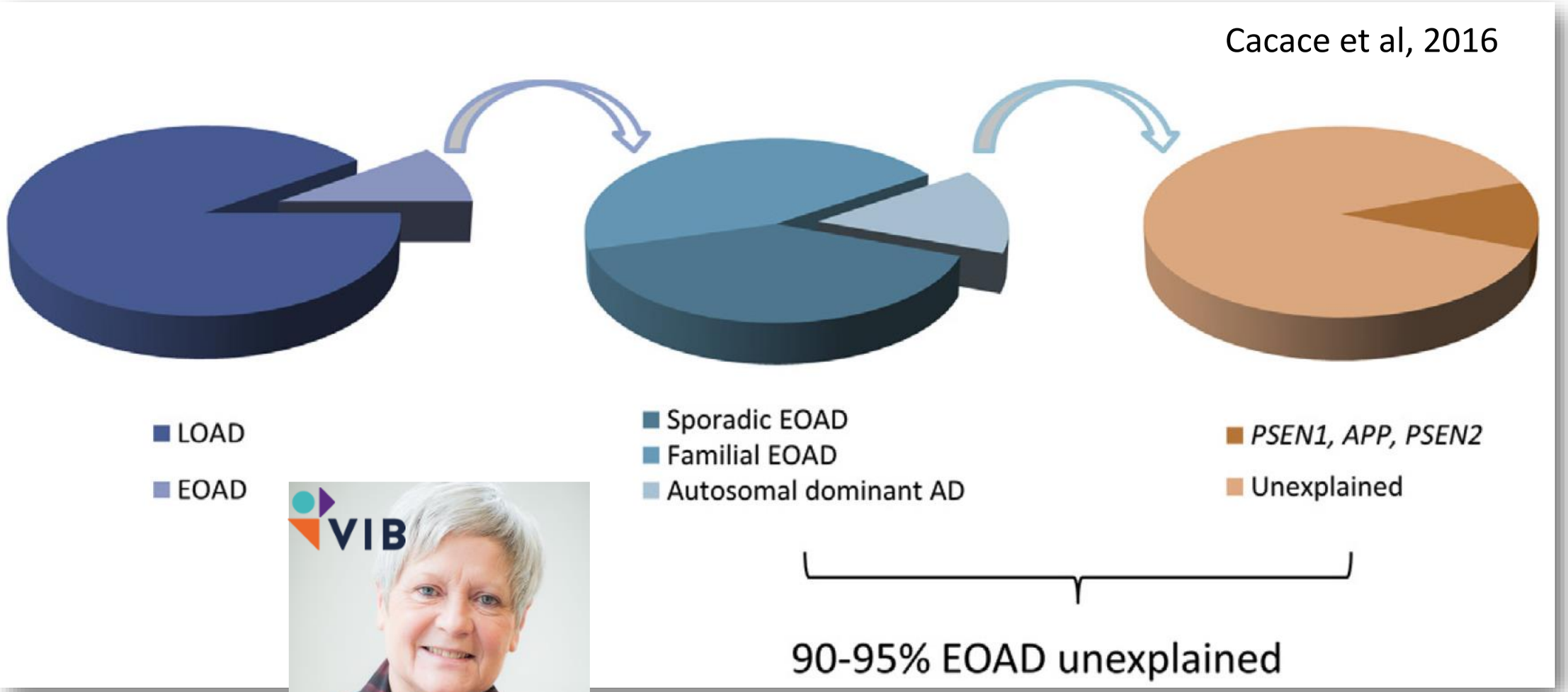
ALZHEIMER'S DISEASE - GENETICS

Cacace et al, 2016



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Christine Van Broeckhoven

ALZHEIMER'S DISEASE - GENETICS

Table 1
Genetic heterogeneity in Alzheimer's disease (AD): Known causal early-onset AD gene

Gene	Chromosome	Inheritance	Gene identification	Mutation spectrum	Mutations (N)
APP	21q21.1–21q21.3	Autosomal dominant Autosomal recessive Protective	Linkage analysis	Missense Gene Duplication Amino acid deletion	54*
PSEN1	14q24.3	Autosomal dominant *de novo*	Linkage analysis	Missense Small indels Genomic deletions	215
PSEN2	1q31–q42	Autosomal dominant	Linkage and homology mapping	Missense	31

*The total number of *APP* mutations includes two causal recessive mutations.

Cacace et al, 2016

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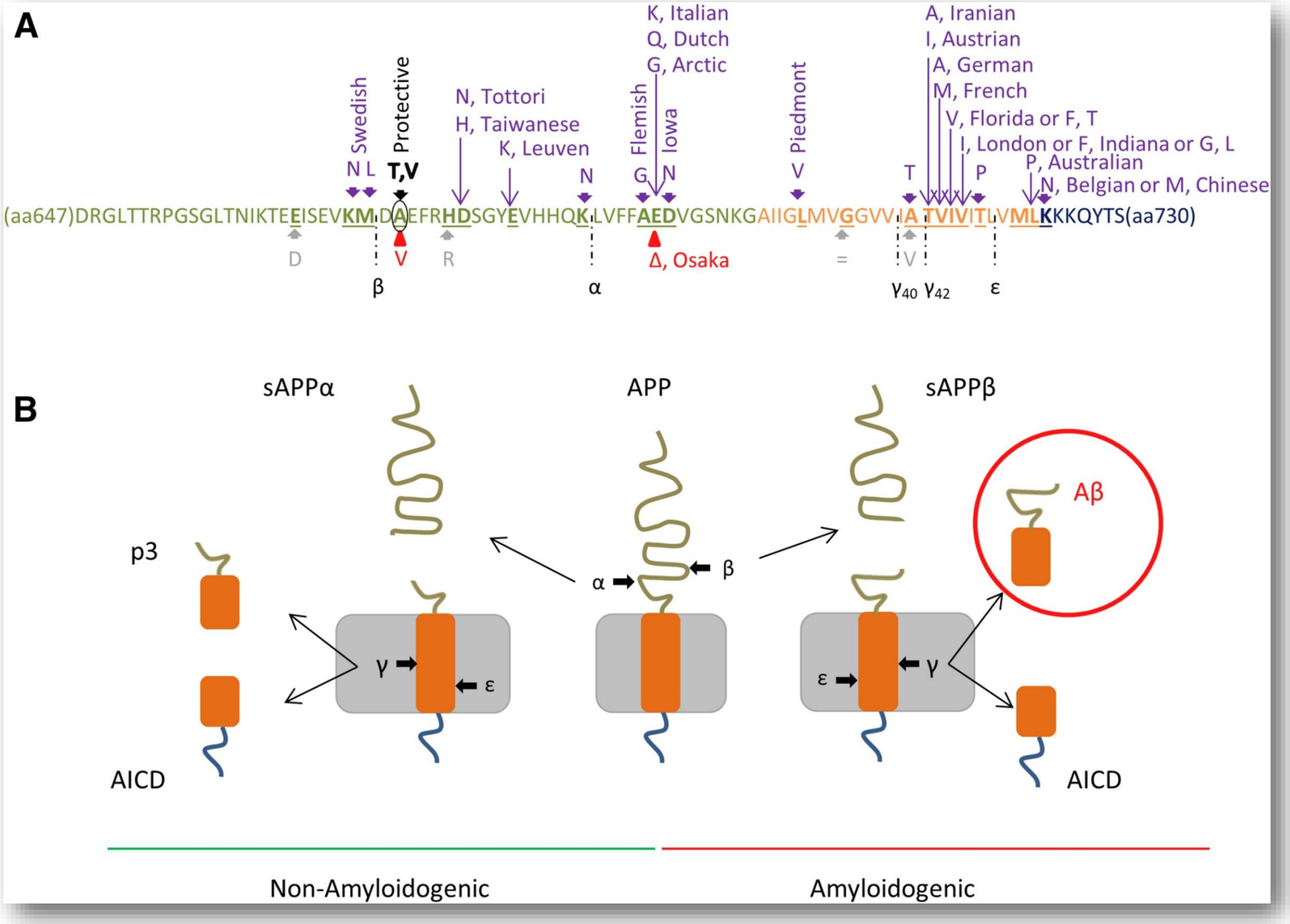
ALZHEIMER'S DISEASE - APP



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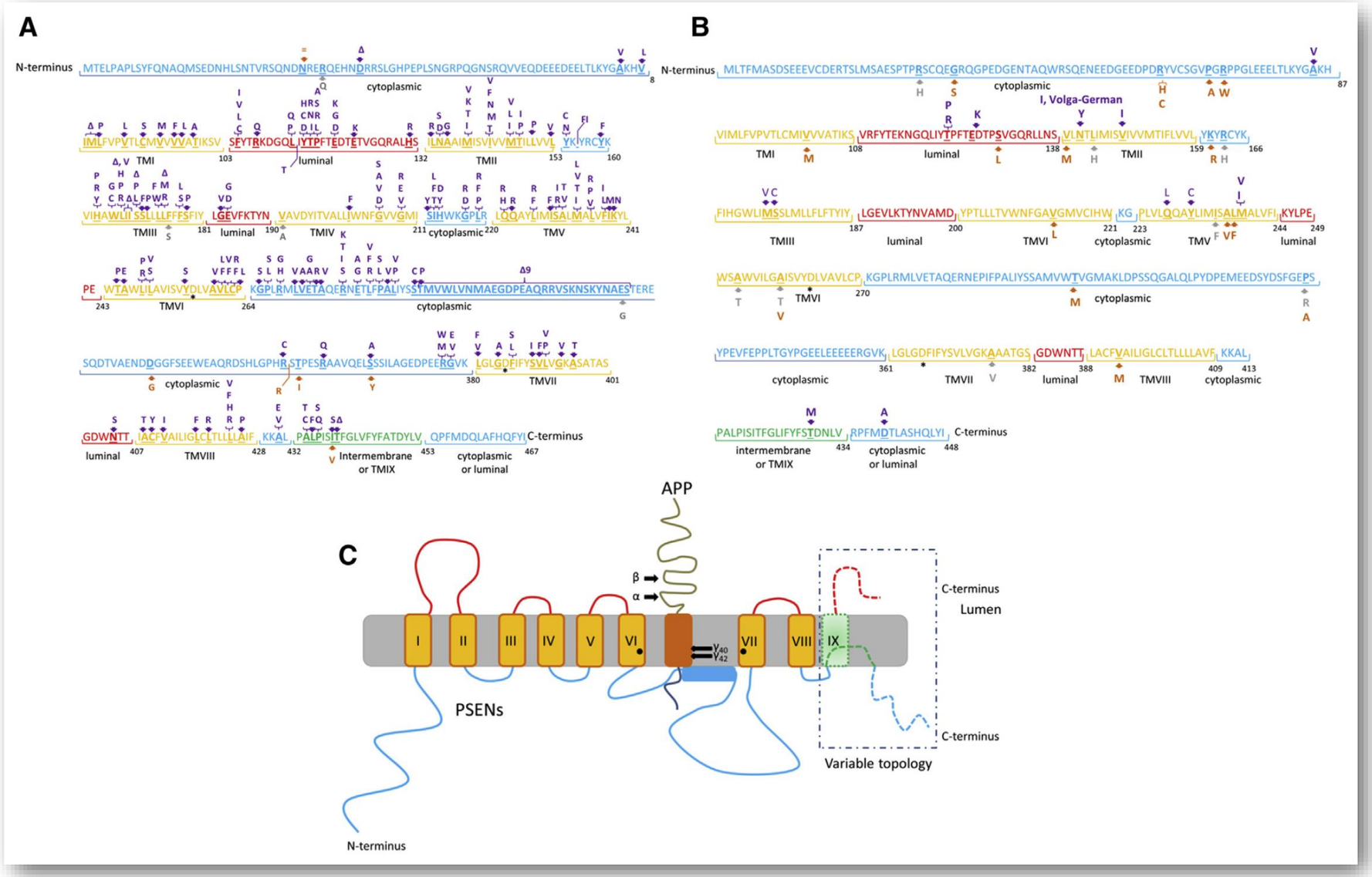
Cacace et al, 2016

ALZHEIMER'S DISEASE – PSEN1/2



Cacace et al, 2016

ALZHEIMER'S DISEASE – APP - PSEN1/2 LINK

NATURE | VOL 391 | 22 JANUARY 1998

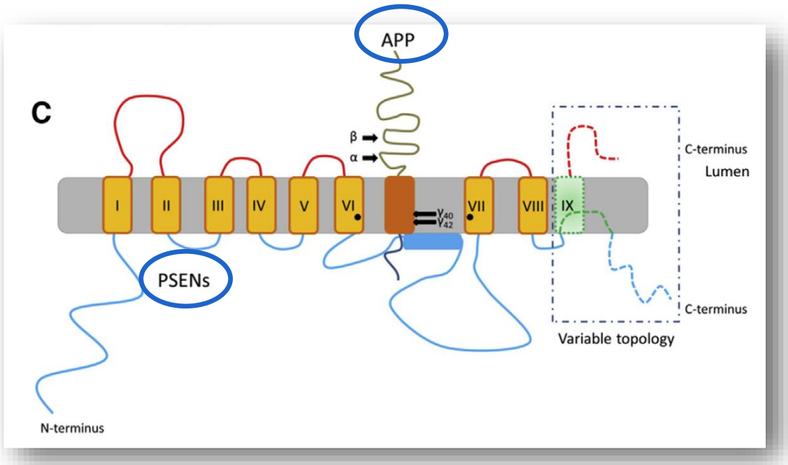
Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein

Bart De Strooper*†, Paul Saftig†‡, Katleen Craessaerts*, Hugo Vanderstichele§, Gundula Guhde‡, Wim Annaert*, Kurt Von Figura‡ & Fred Van Leuven*

* *Experimental Genetics Group, Flemish Institute for Biotechnology (VIB4), Center for Human Genetics, K.U.Leuven, Belgium*
§ *Innogenetics NV, Industriepark Zw.7, 9057 Gent, Belgium*
‡ *Zentrum Biochemie und Molekular Zellbiologie, Abteilung Biochemie II, Universität Göttingen, 37073 Göttingen, Germany*
† *These authors contributed equally to this work.*

Point mutations in the presenilin-1 gene (*PS1*) are a major cause of familial Alzheimer's disease. They result in a selective increase in the production of the amyloidogenic peptide amyloid-β(1–42) by proteolytic processing of the amyloid precursor protein (APP)[1–4]. Here we investigate whether PS1 is also involved in normal APP processing in neuronal cultures derived from PS1-deficient mouse embryos. Cleavage by α- and β-secretase[5] of the extracellular domain of APP was not affected by the absence of PS1, whereas cleavage by γ-secretase of the transmembrane domain of APP was prevented, causing carboxyl-terminal fragments of APP to accumulate and a fivefold drop in the production of amyloid peptide. Pulse-chase experiments indicated that PS1 deficiency specifically decreased the turnover of the membrane-associated fragments of APP. As in the regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor[6], PS1 appears to facilitate a proteolytic activity that cleaves the integral membrane domain of APP. Our results indicate that mutations in *PS1* that manifest clinically cause a gain of function and that inhibition of PS1 activity is a potential target for anti-amyloidogenic therapy in Alzheimer's disease.

Bart De Strooper



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ALZHEIMER'S DISEASE – APP - PSEN1/2 LINK

Genetic counseling

- first degree relatives of individuals with sporadic AD have about a 20% lifetime risk of developing AD

- presumably, when several individuals in a family have AD, the risk is further increased

- EOFAD is inherited in an autosomal dominant manner The risk to offspring of individuals with EOFAD is 50%

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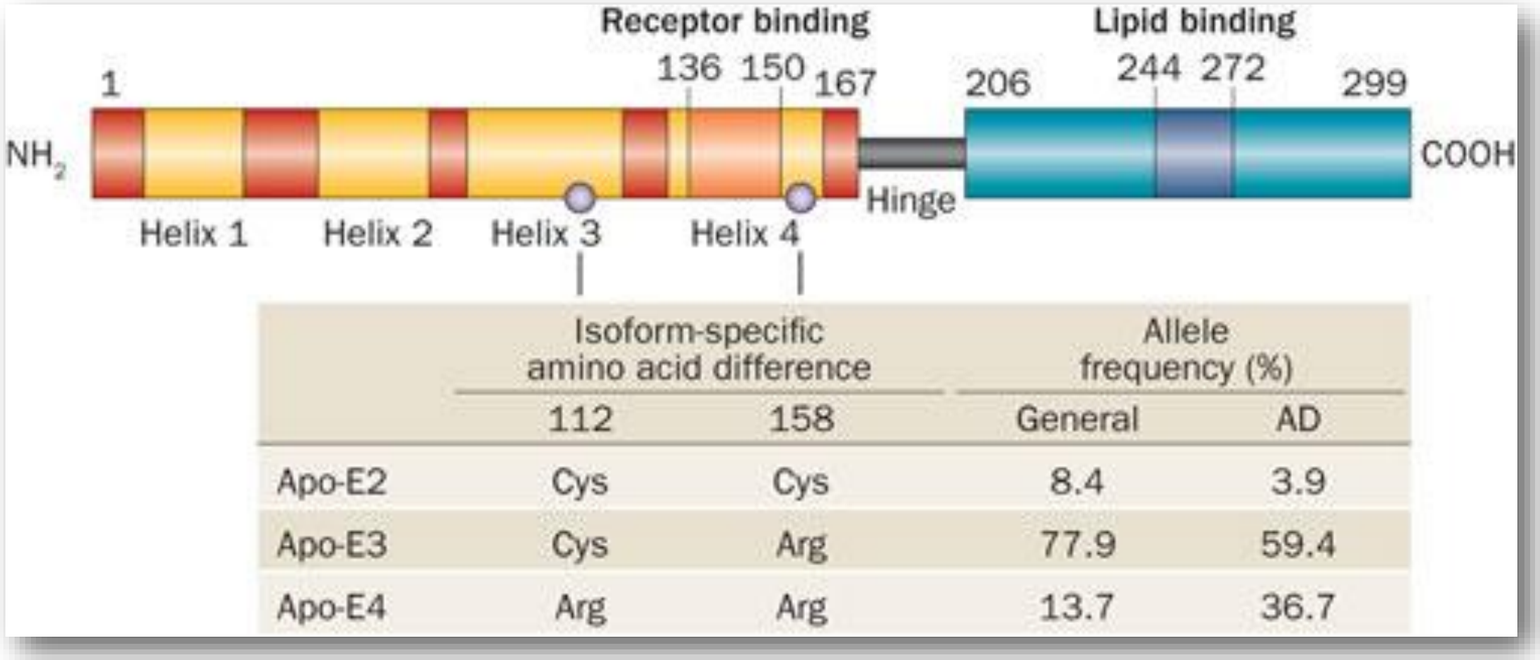
LATE-ONSET ALZHEIMER'S DISEASE GENETICS: APOE

Liu et al, 2013



	Isoform-specific amino acid difference		Allele frequency (%)	
	112	158	General	AD
Apo-E2	Cys	Cys	8.4	3.9
Apo-E3	Cys	Arg	77.9	59.4
Apo-E4	Arg	Arg	13.7	36.7

Genotype	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Disease Risk	40% less likely	40% less likely	2.6 times more likely	Average risk	3.2 times more likely	14.9 times more likely

Credit: alzdiscovery.org/

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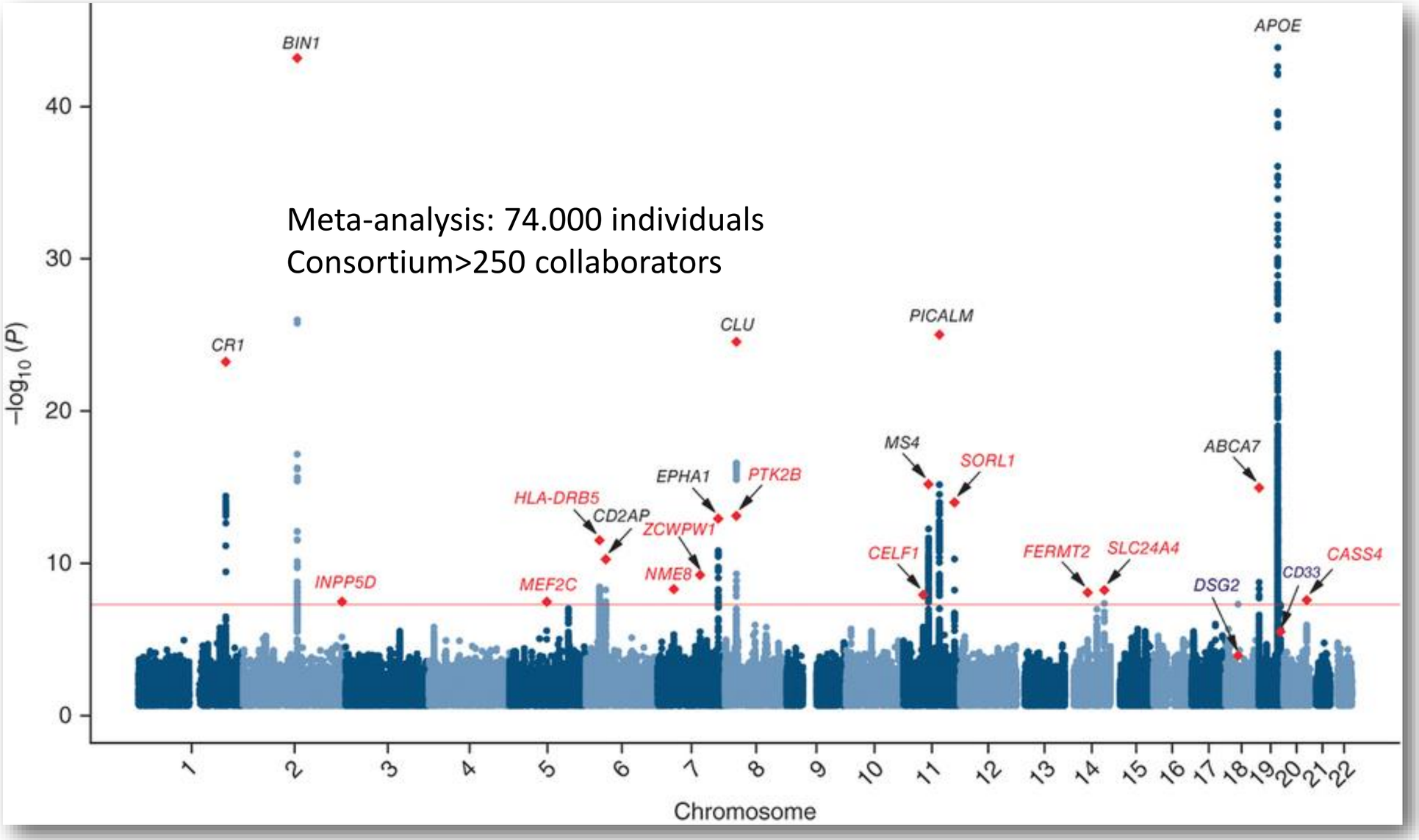
LATE-ONSET ALZHEIMER'S DISEASE GENETICS: GWAS



Lambert et al, Nat Genet 2013

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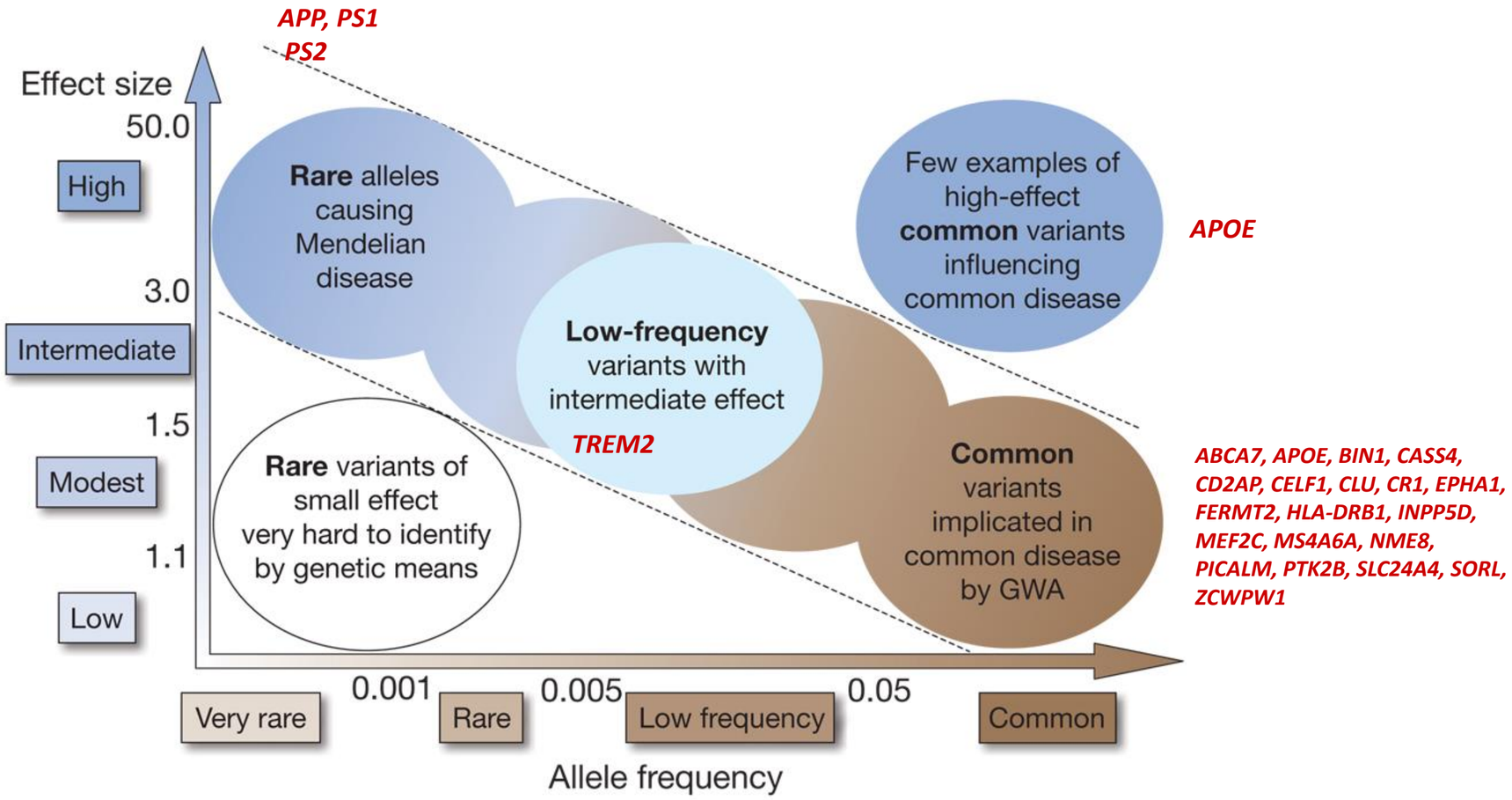
ALZHEIMER'S DISEASE GWAS – GENETIC LANDSCAPE



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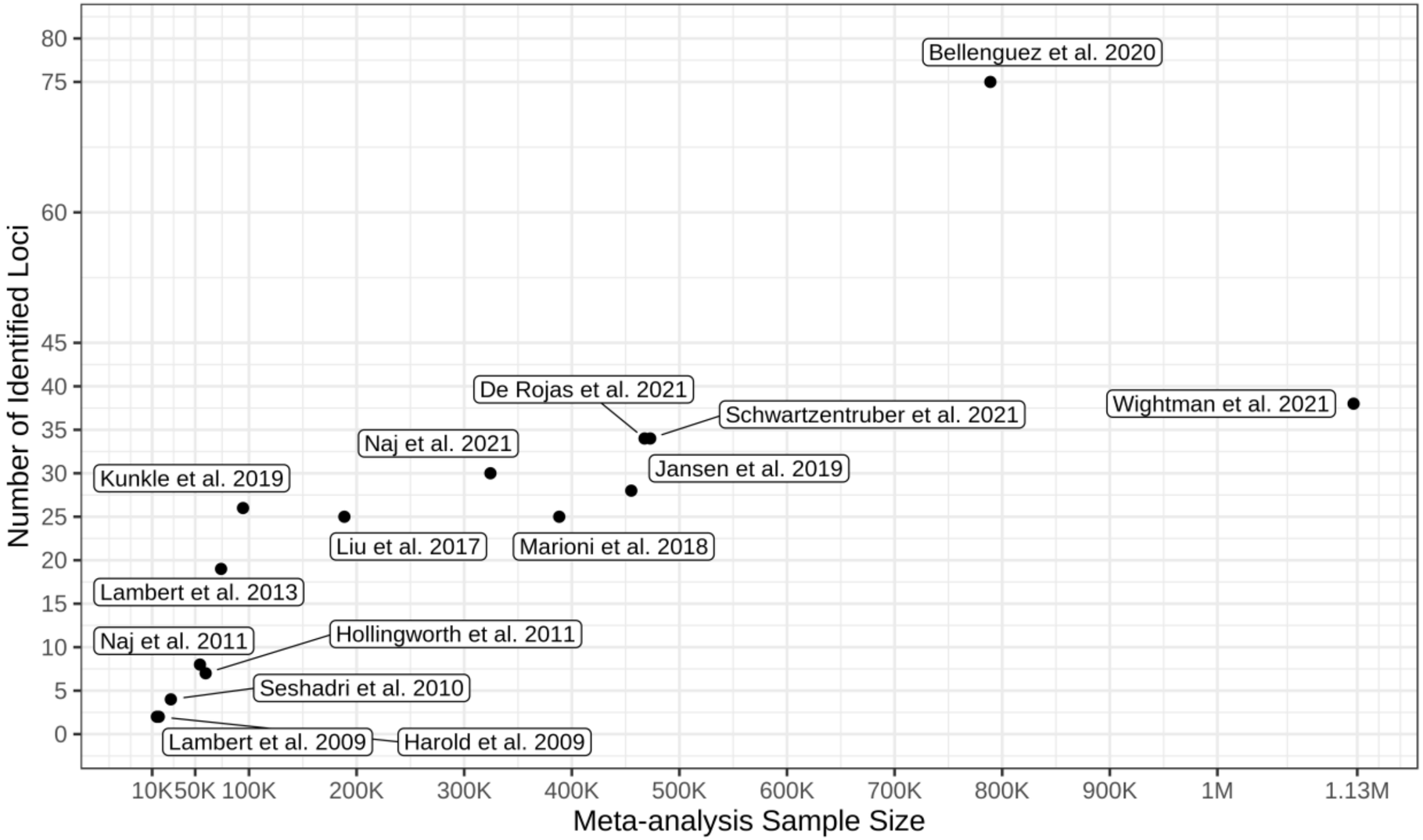
Less than 1% of the cases are monogenic forms.
The genetic attributable risk has been estimated between 60 and 80% and to date, 22 loci have been associated with AD risk.

ALZHEIMER'S DISEASE GWAS



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ALZHEIMER'S DISEASE PATHOGENESIS

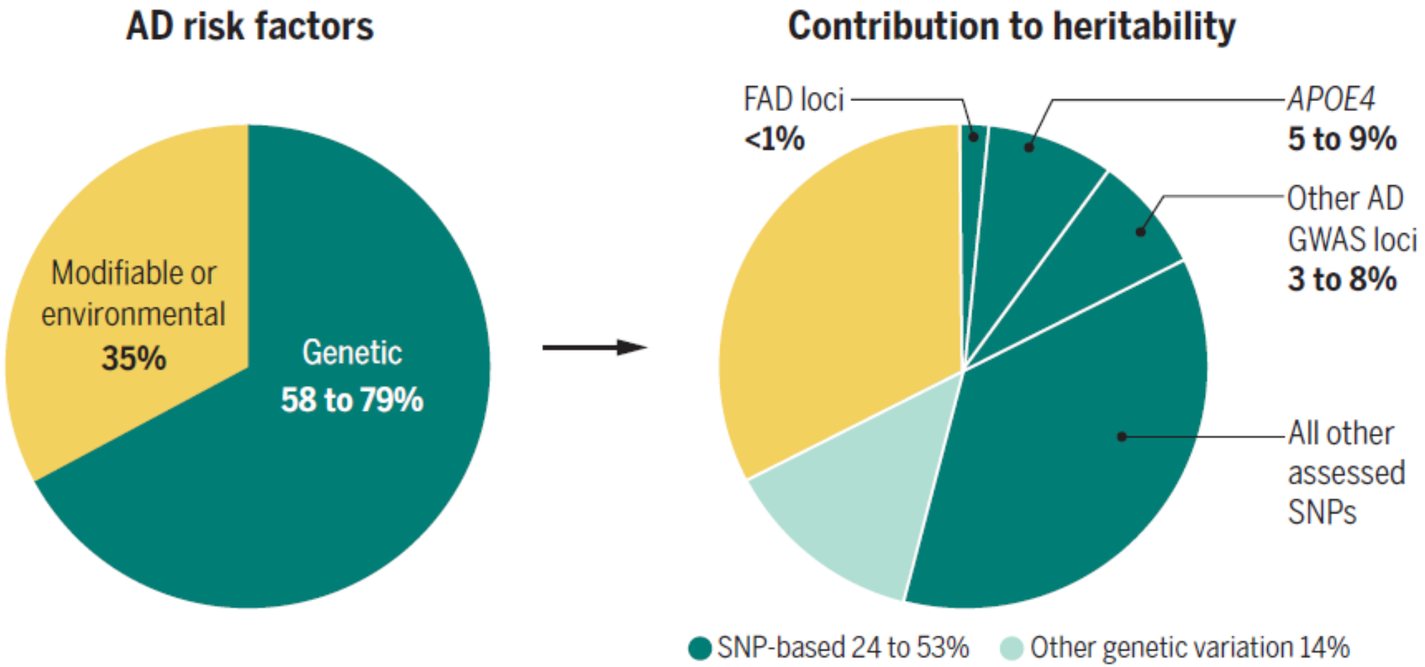

Fig. 1. Risk factors and heritability for AD. Whereas 35% of lifetime risk for AD is composed of modifiable or environmental risk factors, 58 to 79% of AD risk is genetic. The genetics of AD can be broken down into SNP-based heritability and other types of genetic variation, including rare variants, structural and copy-number variation, duplications, SNP×SNP interaction, dominance, and so on. FAD, familial AD.

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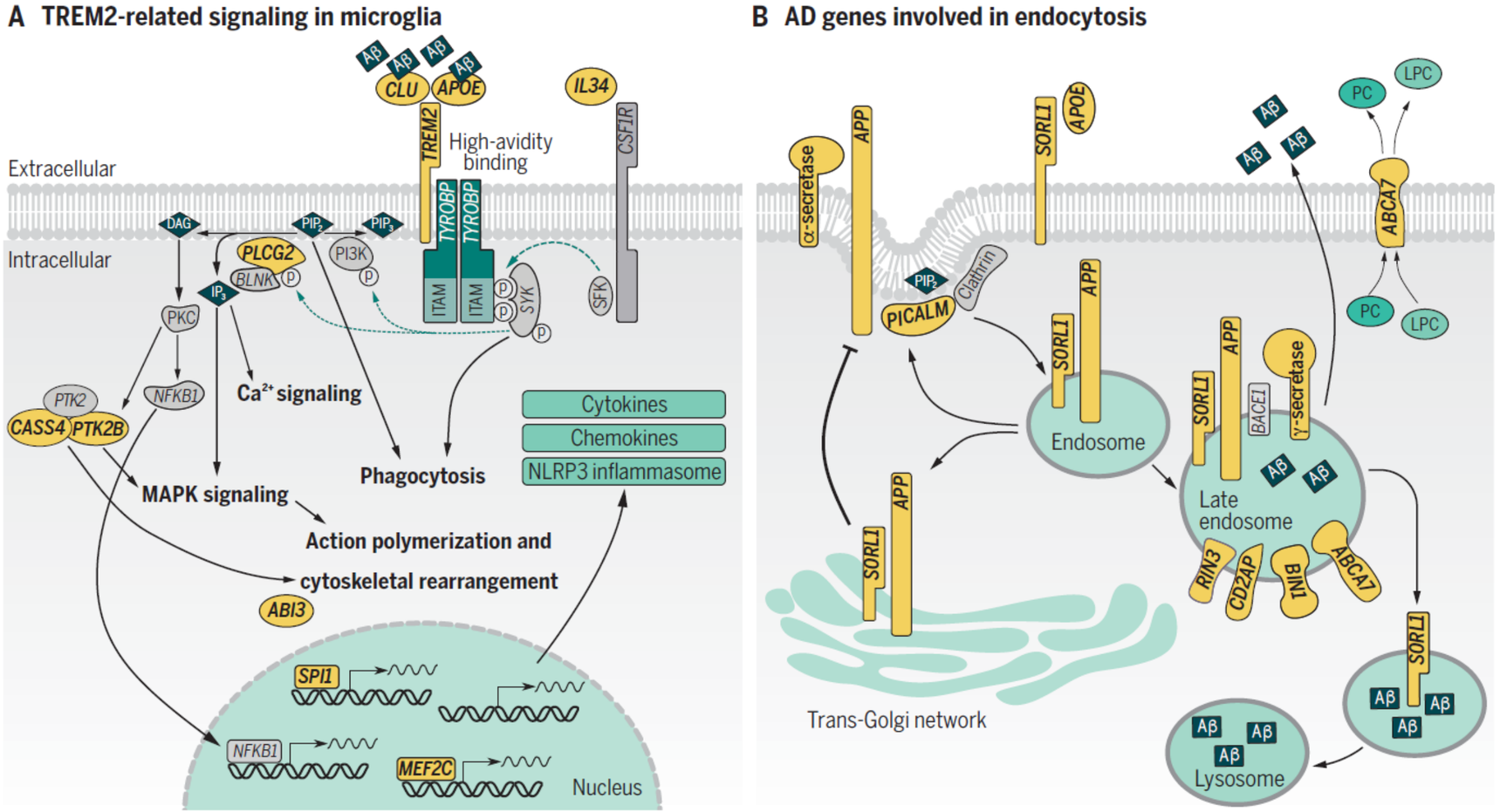
Sierksma *et al.*, *Science* **370**, 61–66 (2020)

ALZHEIMER'S DISEASE PATHOGENESIS



Sierksma *et al.*, *Science* **370**, 61–66 (2020)

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ALZHEIMER'S DISEASE GWAS – THERAPEUTIC STRATEGIES

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Onder andere in China en de Verenigde Staten is het medicijn wel goedgekeurd.
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Beperkte groep patiënten mag Alzheimer-medicijn Leqembi dan toch nemen

Het Europees Geneesmiddelenagentschap EMA geeft nu toch toestemming om het Alzheimer-medicijn Leqembi op de markt te brengen, voor een beperkte groep patiënten. Het medicijn kan de ziekte vertragen. 3 maanden geleden verbood Europa Leqembi nog, vanwege de mogelijke bijwerkingen. In de Verenigde Staten en Groot-Brittannië is het wel toegelaten.

Belga, Mariska Schalck
do 14 nov 19:32

OUTLINE

- Introduction
- Alzheimer’s disease
- **Related disorders: frontotemporal dementia –ALS spectrum**

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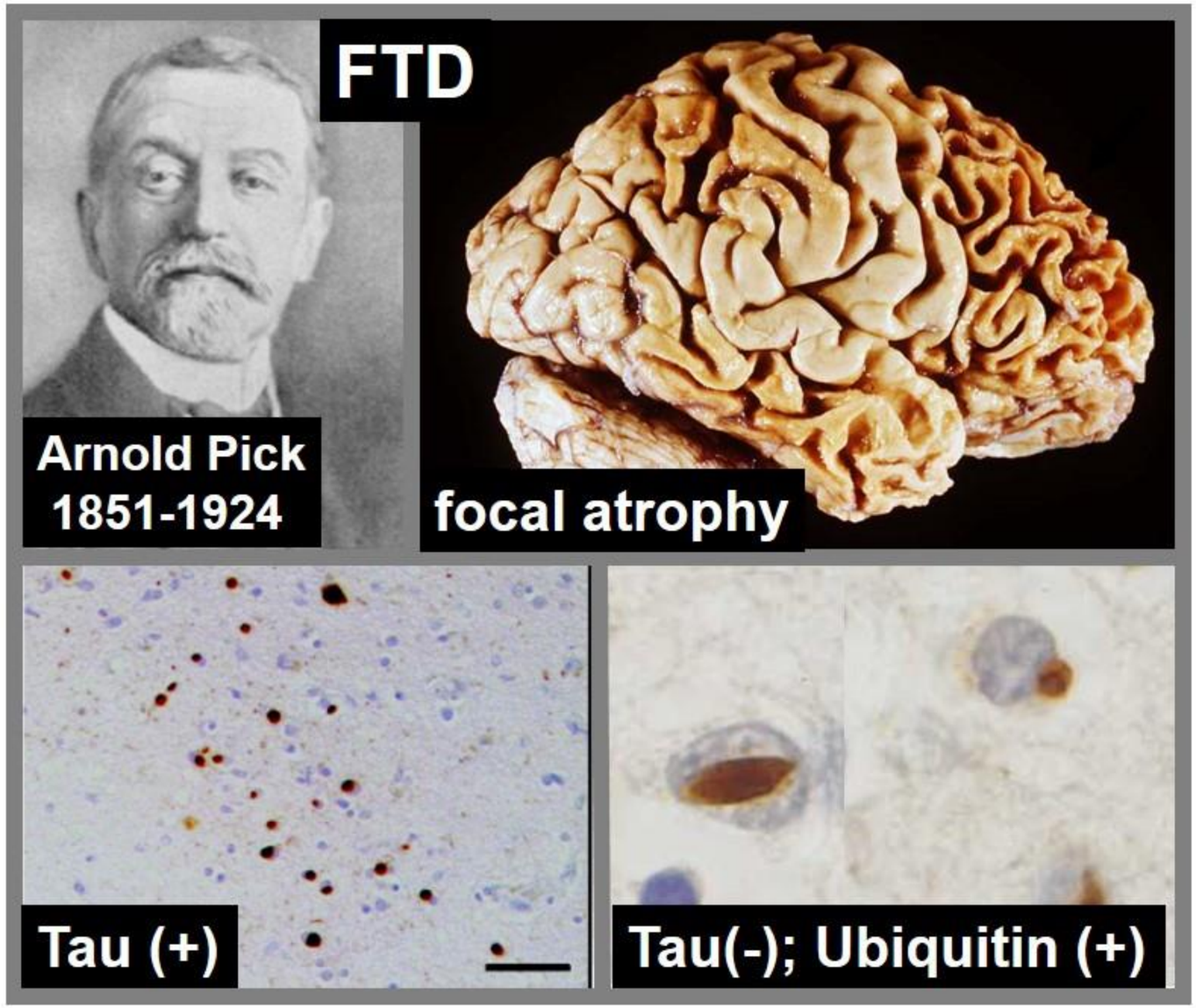
FTD – ALS SPECTRUM



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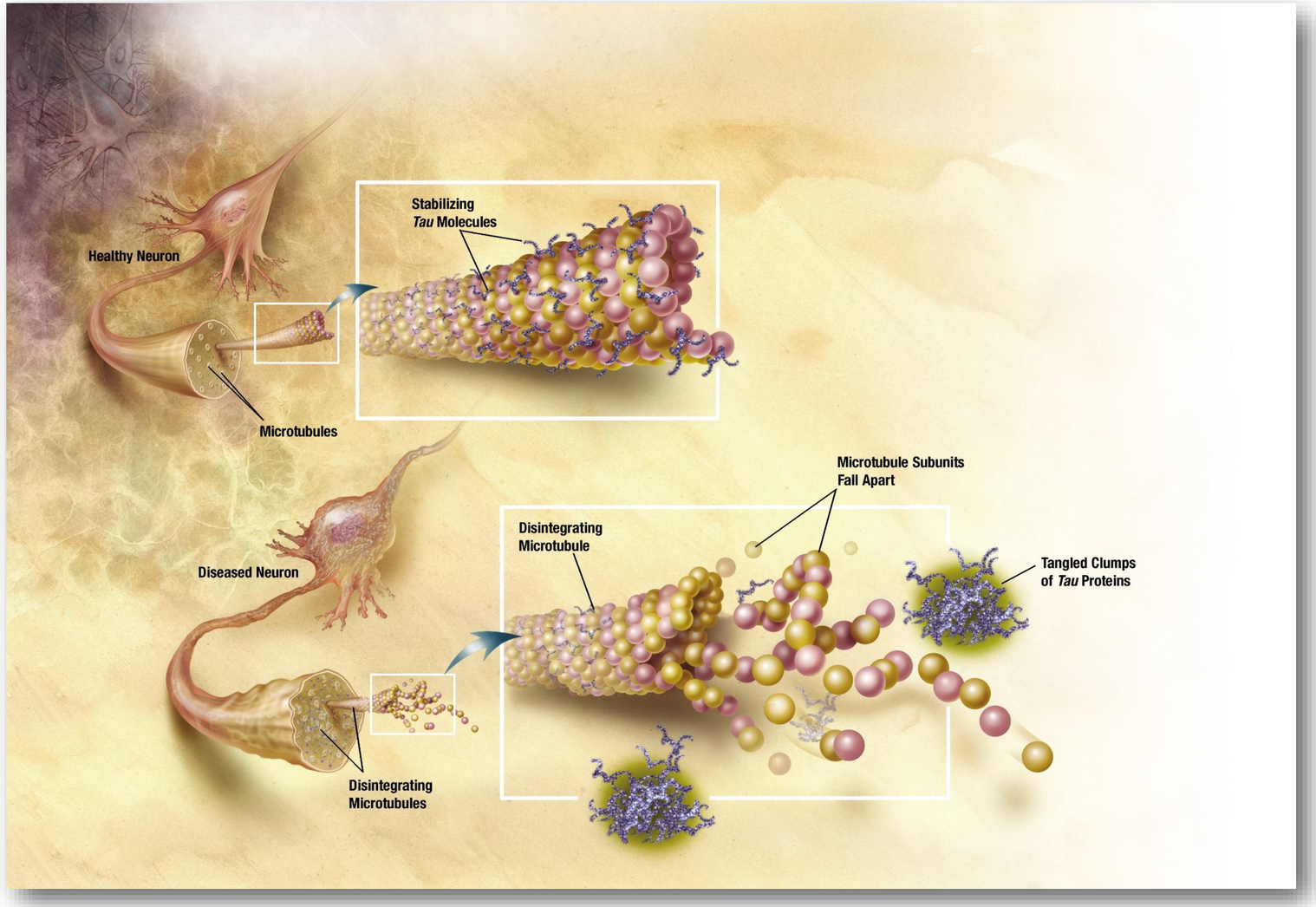
FTD – ALS SPECTRUM



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Although tau neurofibrillary tangles appear to be one of the causes of the neuronal degeneration in AD, mutations in the tau gene are associated not with AD, but with another autosomal dominant dementia, FTD

MAJOR NEURODEGENERATIVE DISEASES = PROTEINOPATHIES

- Parkinson's disease:
  - Lewy bodies (**a-synuclein**)
- Alzheimer's disease:
  - Amyloid plaques (**Ab peptide**)
  - Tau tangles (**tau**)
- Frontotemporal dementia
  - Tau tangles/Pick bodies (**tau**)
  - Ubiquitin(+) inclusions (**TDP-43**)
- Amyotrophic lateral sclerosis 2006
  - Ubiquitin(+) inclusions (**TDP-43)**

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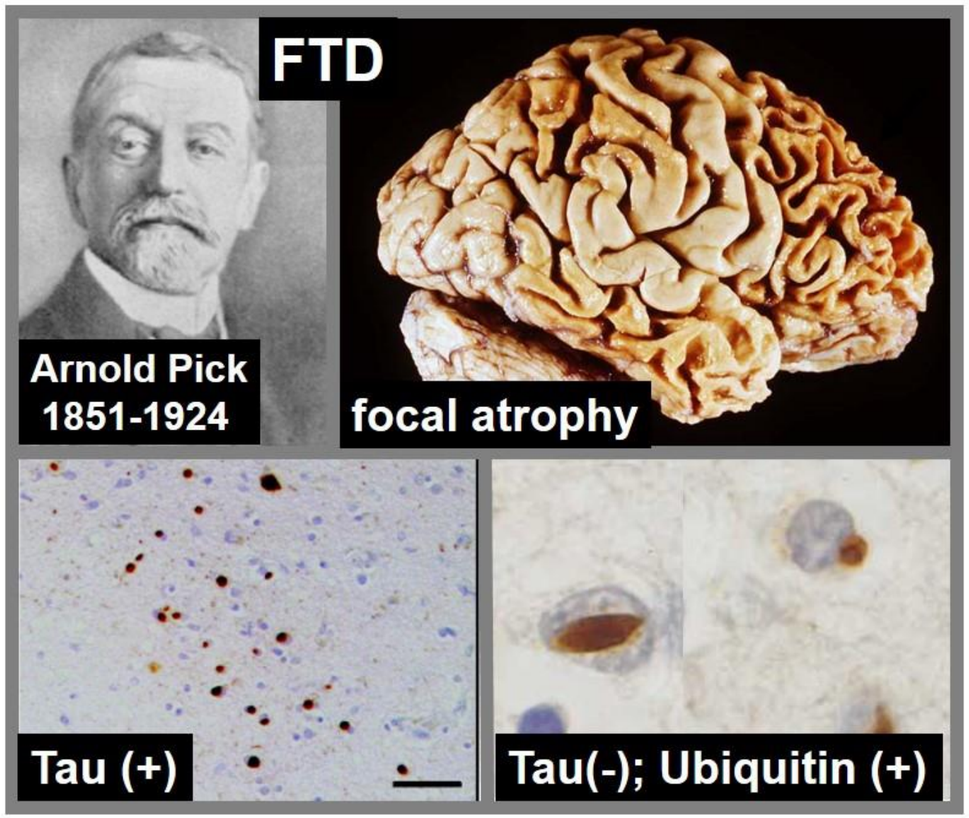
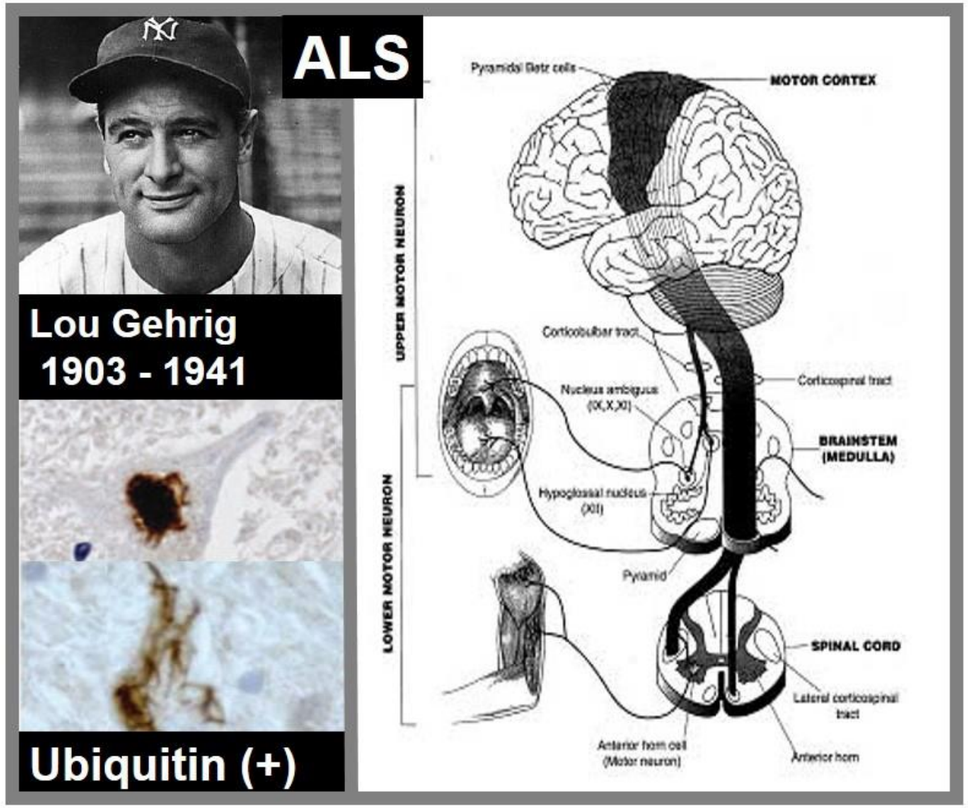
FTD – ALS SPECTRUM





TDP-43

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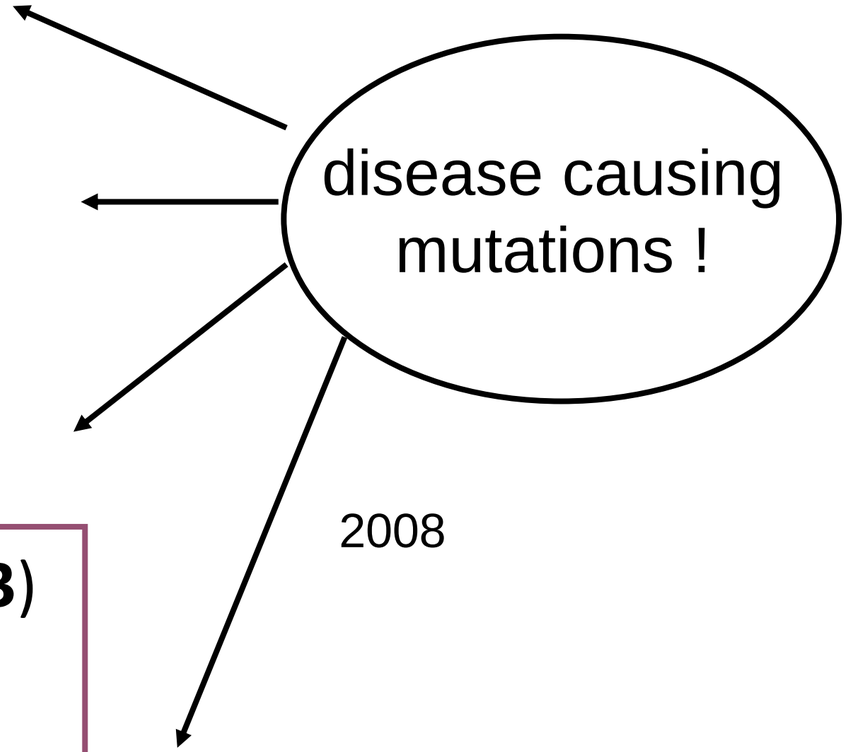
MAJOR NEURODEGENERATIVE DISEASES = PROTEINOPATHIES

- Parkinson's disease:
  - Lewy bodies (**a-synuclein**)
- Alzheimer's disease:
  - Amyloid plaques (**Aβ peptide**)
  - Tau tangles (**tau**)
- Frontotemporal dementia
  - Tau tangles/Pick bodies (**tau**)
  - Ubiquitin(+) inclusions (**TDP-43**)
- Amyotrophic lateral sclerosis
  - Ubiquitin(+) inclusions (**TDP-43)**



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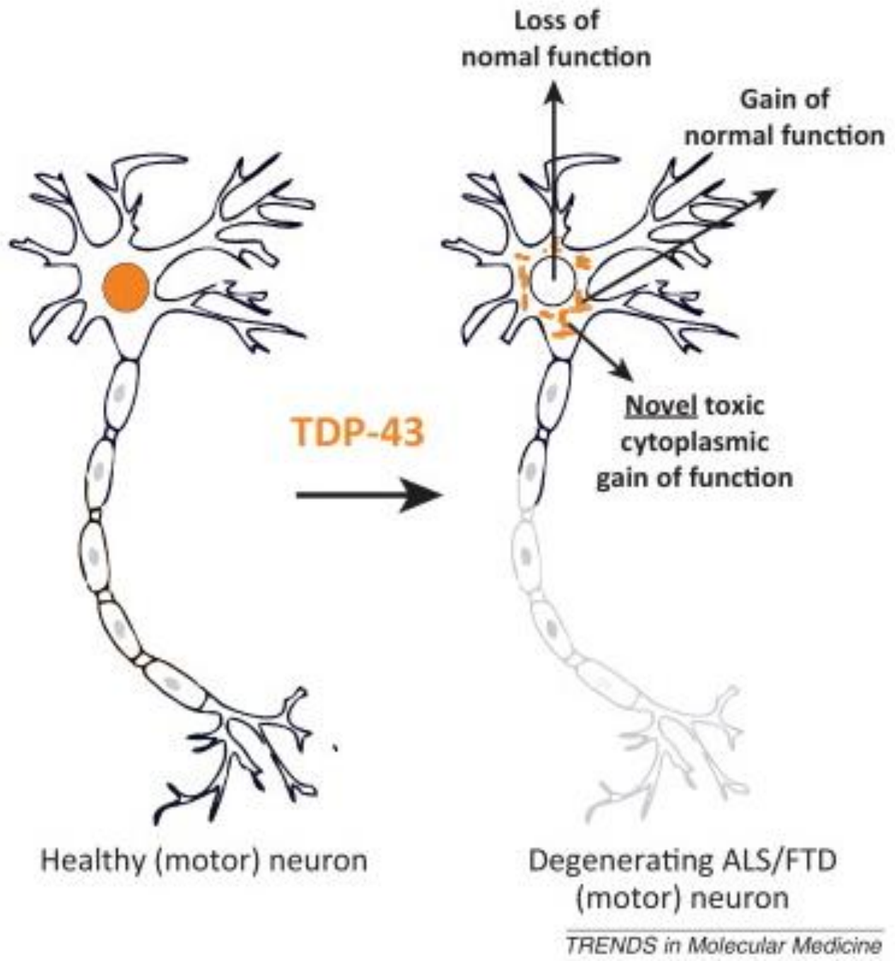
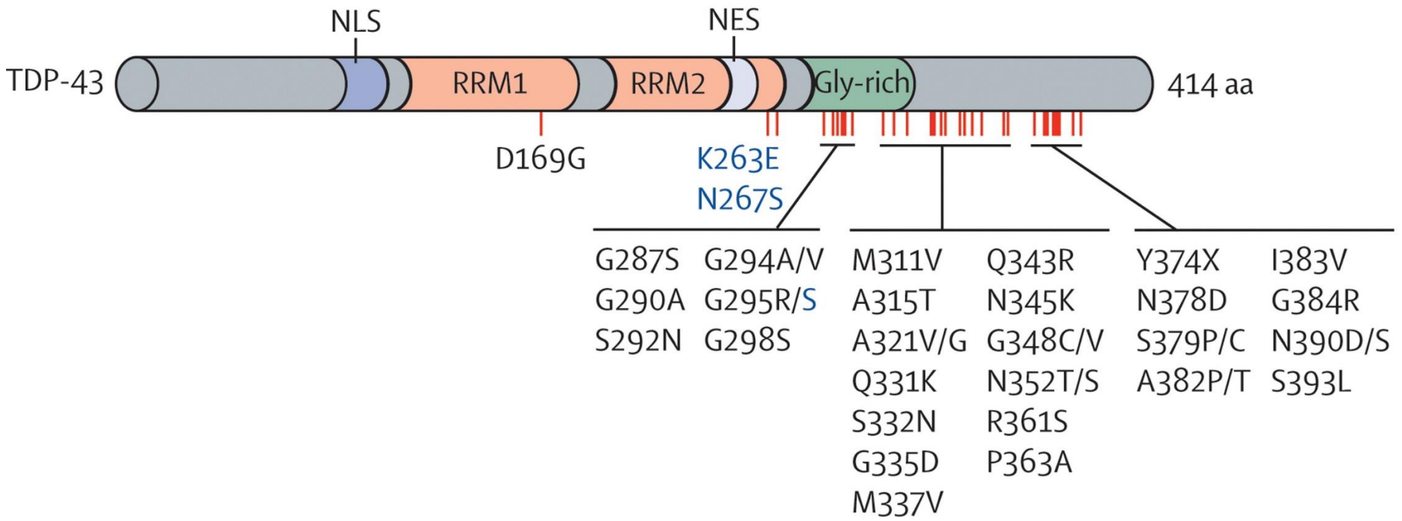
FTD – ALS SPECTRUM: TDP-43





ALS-causing mutations

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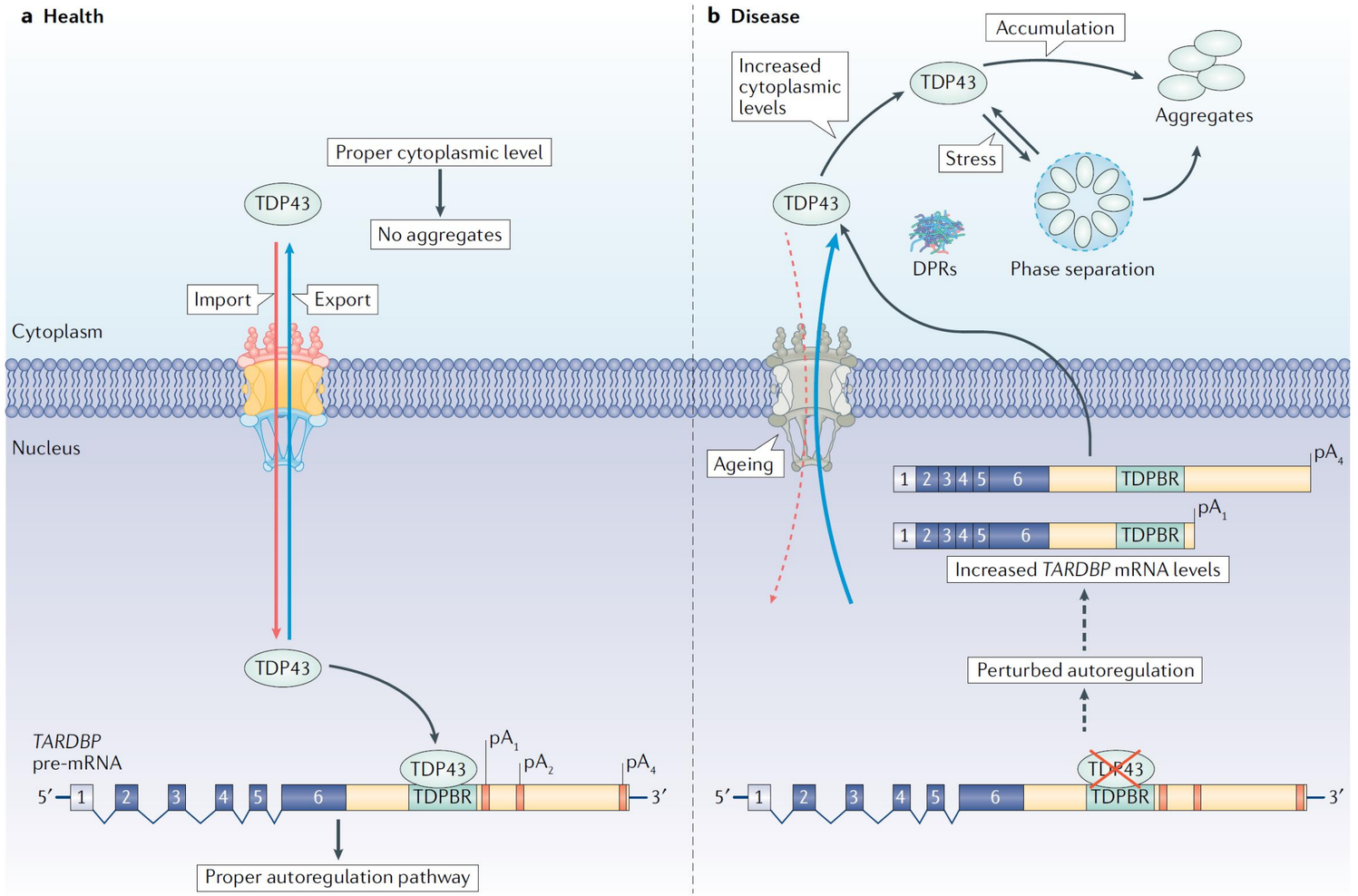
FTD – ALS SPECTRUM: TDP-43



Triad of TDP43 control in neurodegeneration: autoregulation, localization and aggregation

Paraskevi Tziortzouda[1,2], Ludo Van Den Bosch[1,2]✉ and Frank Hirth[3]✉

NATURE REVIEWS | NEUROSCIENCE

VOLUME 22 | APRIL 2021 |

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ALS-FTD GENETICS

Table 1 Major ALS/FTD genes

ALS/FTD	Gene	Mutation	Protein/function	Disease contribution
ALS	SOD1	Missense	Superoxide dismutase 1/oxidative stress	fALS 12%, sALS ~1%
ALS	OPN		Optineurin/vesicle trafficking	fALS <1%, sALS <1%
ALS/FTD	C9orf72	Non-coding GGGGCC expansion	C9orf72/GDP-GTP nucleotide exchange factor	fALS 40%, sALS 7% sFTD 25%, sFTD 6%
ALS/FTD	TARDBP	Missense/nonsense	TDP-43/RNA-binding, processing	fALS 5%, sALS <1% fFTD 1%
ALS/FTD	FUS	Missense/nonsense	FUS/RNA-binding, processing	fALS 4%, sALS <1%
ALS/FTD	VCP	Missense	Valosin-containing protein/proteasome, vesicle trafficking	fALS 1% fFTD <1%
ALS/FTD	UBQLN1	Missense	Ubiquilin-1/protein degradation	X linked ALS/FTD <1%, sALS 2%
ALS/FTD	SQSTM1	Missense/deletion	p62/protein degradation	fALS ~1%, sALS 4% fFTD 2%
ALS/FTD	CHMP2B	Missense	Charged multivesicular protein 2B/vesicle trafficking	fFTD <1%
FTD	MAPT	Missense and splice-site	Tau/microtubule binding and stabilisation	fFTD ~10%
FTD	GRN	Missense	Granulin/tissue repair	fFTD ~20%, sFTD 5%

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FUS, fused in sarcoma; f, familial; GRN, *granulin*; MAPT, microtubule-associated protein tau; s, sporadic; VCP, valosin-containing protein.

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ALS-FTD GENETICS: C9ORF72 HEXANUCLEOTIDE EXPANSIONS

Neuron 2011

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,*]

Rosa Rademakers

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

Alan E. Renton,[1,38] Elisa Majounie,[2,38] Adrian Waite,[3,38] Javier Simón-Sánchez,[4,5,38] Sara Rollinson,[6,38] J. Raphael Gibbs,[7,8,38] Jennifer C. Schymick,[1,38] Hannu Laaksovirta,[9,38] John C. van Swieten,[4,5,38] 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,[8] Danyah Trabzuni,[8] Rita J. Guerreiro,[8] 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,[8] Andrew Singleton,[2] Nigel M. Williams,[3,38] Peter Heutink,[4,38] Stuart Pickering-Brown,[6,38] Huw R. Morris,[3,36,37,38] Pentti J. Tienari,[9,38] and Bryan J. Traynor[1,14,38,*]

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ALS-FTD GENETICS: C9ORF72 HEXANUCLEOTIDE EXPANSIONS

A *C9orf72* promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study

Ilse Gijselinck, Tim Van Langenhove, Julie van der Zee, Kristel Sleegers, Stéphanie Philtjens, Gernot Kleinberger, Jonathan Janssens, Karolien Bettens, Caroline Van Cauwenberghe, Sandra Pereson, Sebastiaan Engelborghs, Anne Sieben, Peter De Jonghe, Rik Vandenberghe, Patrick Santens, Jan De Bleecker, Githa Maes, Veerle Bäumer, Lubina Dillen, Geert Joris, Ivy Cuijt, Ellen Corsmit, Ellen Elinck, Jasper Van Dongen, Steven Vermeulen, Marleen Van den Broeck, Carolien Vaerenberg, Maria Mattheijssens, Karin Peeters, Wim Robberecht, Patrick Cras, Jean-Jacques Martin, Peter P De Deyn, Marc Cruts, Christine Van Broeckhoven

Lancet Neurology 2012

Christine Van Broeckhoven

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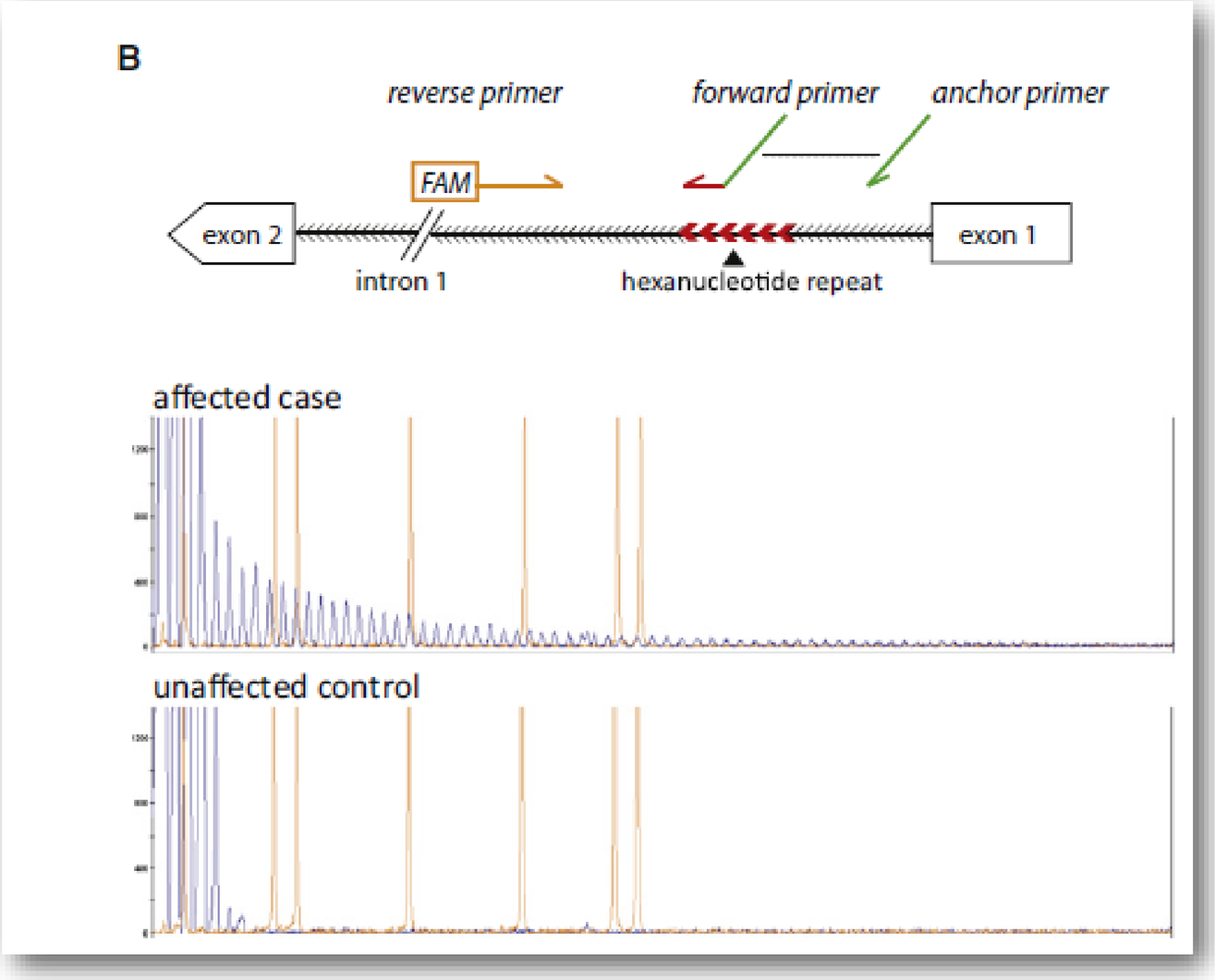
ALS-FTD GENETICS: C9ORF72 HEXANUCLEOTIDE EXPANSIONS



Normal alleles:

<25 G4C2 repeats

Pathogenic (high penetrance):

>65 G4C2 repeats

(up to 4000)

Anticipation ?

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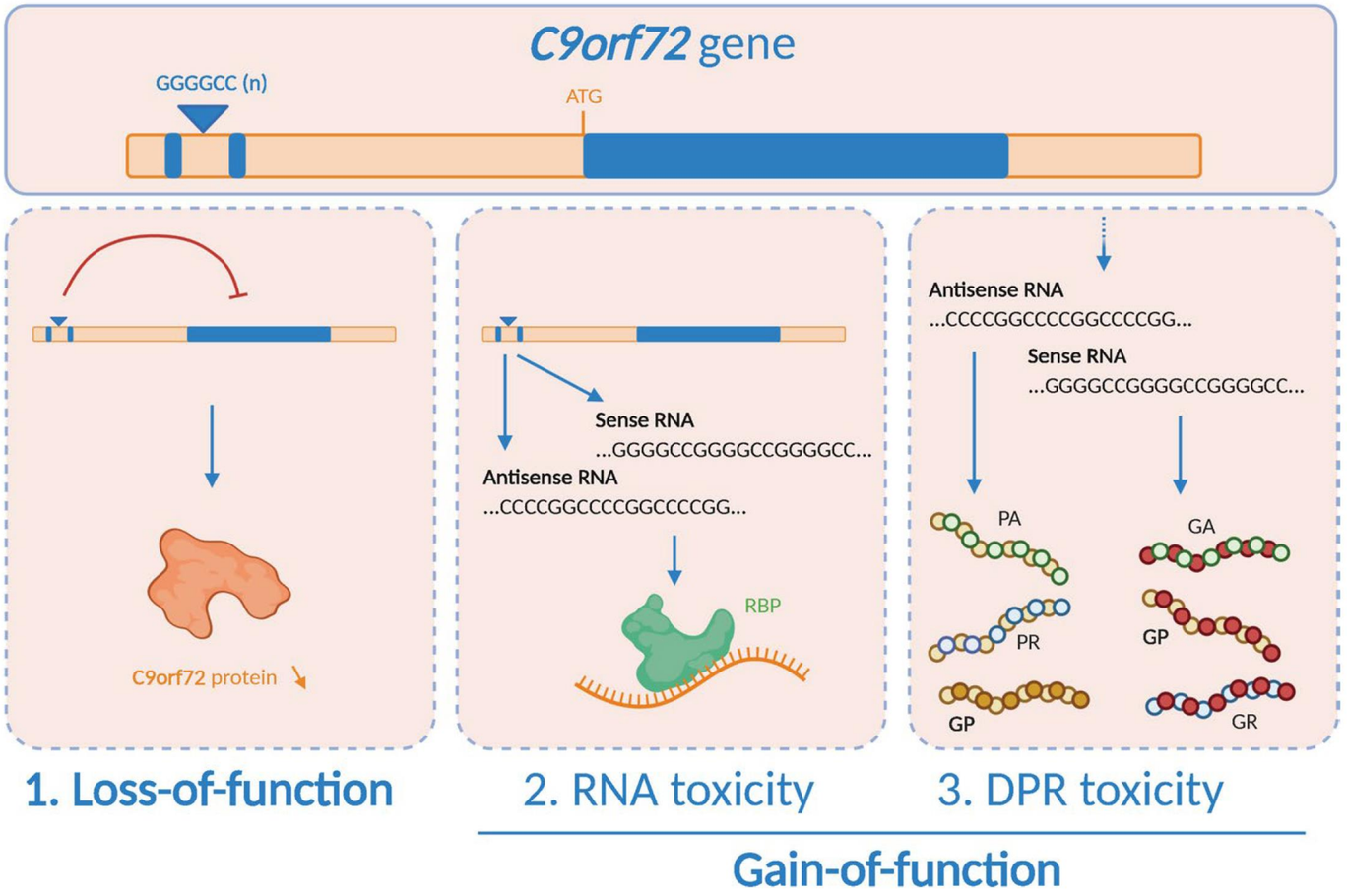
ALS-FTD GENETICS: C9ORF72 HEXANUCLEOTIDE EXPANSIONS



Acta Neuropathologica (2020) 140:625–643
https://doi.org/10.1007/s00401-020-02214-x

REVIEW

C9orf72 loss-of-function: a trivial, stand-alone or additive mechanism in C9 ALS/FTD?

Elke Braems[1,2] · Bart Swinnen[1,2,3] · Ludo Van Den Bosch[1,2]

ALS-FTD GENETICS

Table 1 Major ALS/FTD genes

ALS/FTD	Gene	Mutation	Protein/function	Disease contribution
ALS	SOD1	Missense	Superoxide dismutase 1/oxidative stress	fALS 12%, sALS ~1%
ALS	OPN		Optineurin/vesicle trafficking	fALS <1%, sALS <1%
ALS/FTD	C9orf72	Non-coding GGGGCC expansion	C9orf72/GDP-GTP nucleotide exchange factor	fALS 40%, sALS 7% sFTD 25%, sFTD 6%
ALS/FTD	TARDBP	Missense/nonsense	TDP-43/RNA-binding, processing	fALS 5%, sALS <1% fFTD 1%
ALS/FTD	FUS	Missense/nonsense	FUS/RNA-binding, processing	fALS 4%, sALS <1%
ALS/FTD	VCP	Missense	Valosin-containing protein/proteasome, vesicle trafficking	fALS 1% fFTD <1%
ALS/FTD	UBQLN1	Missense	Ubiquilin-1/protein degradation	X linked ALS/FTD <1%, sALS 2%
ALS/FTD	SQSTM1	Missense/deletion	p62/protein degradation	fALS ~1%, sALS 4% fFTD 2%
ALS/FTD	CHMP2B	Missense	Charged multivesicular protein 2B/vesicle trafficking	fFTD <1%
FTD	MAPT	Missense and splice-site	Tau/microtubule binding and stabilisation	fFTD ~10%
FTD	GRN	Missense	Granulin/tissue repair	fFTD ~20%, sFTD 5%

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; FUS, fused in sarcoma; f, familial; GRN, *granulin*; MAPT, microtubule-associated protein tau; s, sporadic; VCP, valosin-containing protein.

2011
2008
1998
2006

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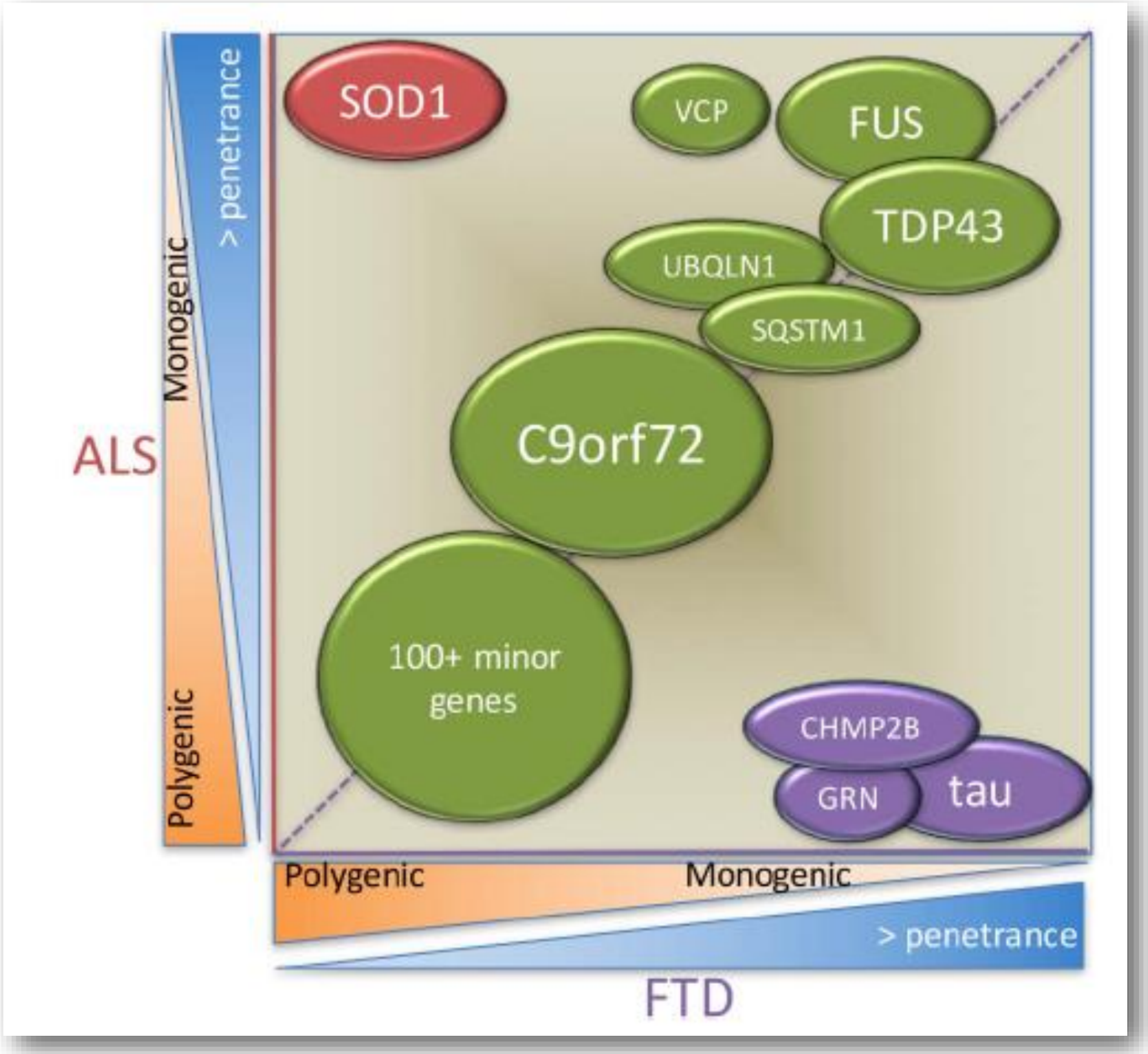
ALS-FTD GENETICS



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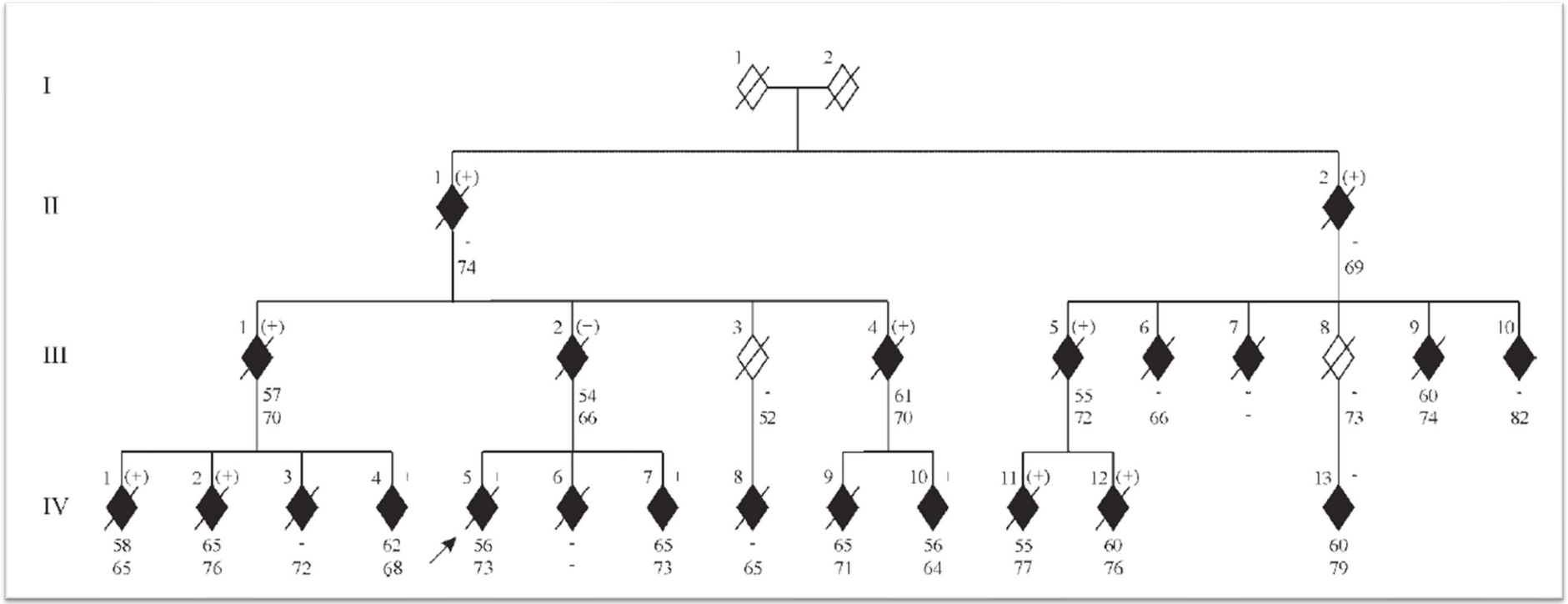
EARLY-ONSET DEMENTIA GENETICS



Rosa Rademakers

Christine Van Broeckhoven

1997 start PhD: “novel genes for early-onset dementia”, first project family AD/G, typical Alzheimer phenotype, negative for *APP*, *PSEN1*, *PSEN2*

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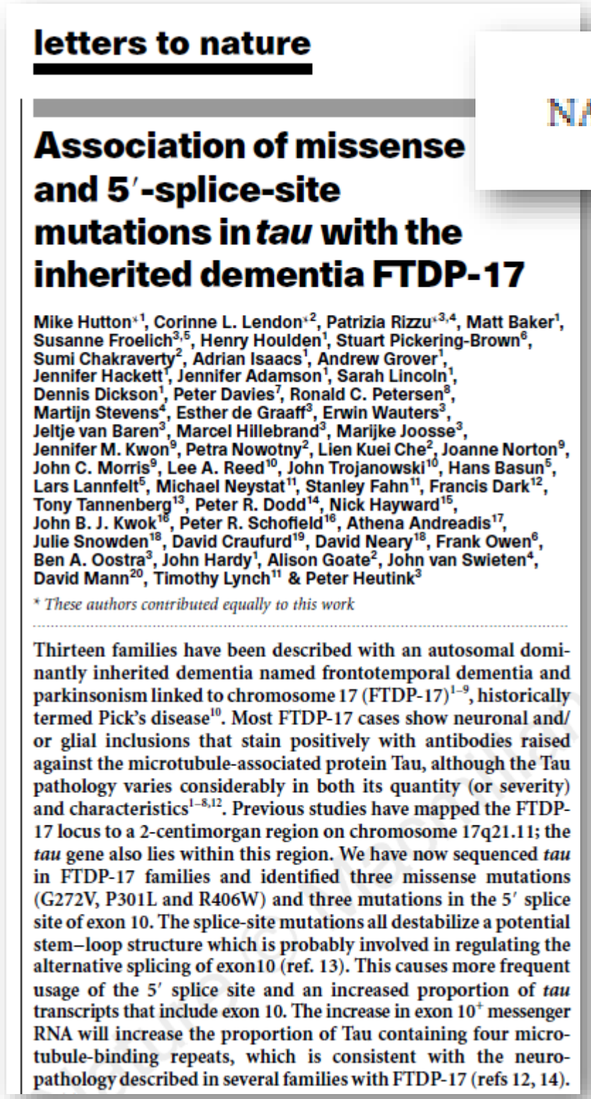

letters to nature

Association of missense and 5′-splice-site mutations in *tau* with the inherited dementia FTDP-17

Mike Hutton*[1], Corinne L. Lendon*[2], Patrizia Rizzu*[3,4], Matt Baker[1], Susanne Froelich[3,5], Henry Houlden[1], Stuart Pickering-Brown[6], Sumi Chakraverty[2], Adrian Isaacs[1], Andrew Grover[1], Jennifer Hackett[1], Jennifer Adamson[1], Sarah Lincoln[1], Dennis Dickson[1], Peter Davies[7], Ronald C. Petersen[8], Martijn Stevens[4], Esther de Graaff[3], Erwin Wauters[3], Jeltje van Baren[3], Marcel Hillebrand[3], Marijke Joosse[3], Jennifer M. Kwon[9], Petra Nowotny[2], Lien Kuei Che[2], Joanne Norton[9], John C. Morris[9], Lee A. Reed[10], John Trojanowski[10], Hans Basun[5], Lars Lannfelt[5], Michael Neystat[11], Stanley Fahn[11], Francis Dark[12], Tony Tannenberg[13], Peter R. Dodd[14], Nick Hayward[15], John B. J. Kwok[16], Peter R. Schofield[16], Athena Andreadis[17], Julie Snowden[18], David Craufurd[19], David Neary[18], Frank Owen[6], Ben A. Oostra[3], John Hardy[1], Alison Goate[2], John van Swieten[4], David Mann[20], Timothy Lynch[11] & Peter Heutink[3]

* *These authors contributed equally to this work*

Thirteen families have been described with an autosomal dominantly inherited dementia named frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)[1–9], historically termed Pick's disease[10]. Most FTDP-17 cases show neuronal and/or glial inclusions that stain positively with antibodies raised against the microtubule-associated protein Tau, although the Tau pathology varies considerably in both its quantity (or severity) and characteristics[1–8,12]. Previous studies have mapped the FTDP-17 locus to a 2-centimorgan region on chromosome 17q21.11; the *tau* gene also lies within this region. We have now sequenced *tau* in FTDP-17 families and identified three missense mutations (G272V, P301L and R406W) and three mutations in the 5′ splice site of exon 10. The splice-site mutations all destabilize a potential stem–loop structure which is probably involved in regulating the alternative splicing of exon10 (ref. 13). This causes more frequent usage of the 5′ splice site and an increased proportion of *tau* transcripts that include exon 10. The increase in exon 10^+ messenger RNA will increase the proportion of Tau containing four microtubule-binding repeats, which is consistent with the neuropathology described in several families with FTDP-17 (refs 12, 14).

NATURE | VOL 393 | 18 JUNE 1998

13 A.D. families with Tau+ neuropathology and clinical presentation of FTD (+ Parkinsonism) linked to chromosome 17

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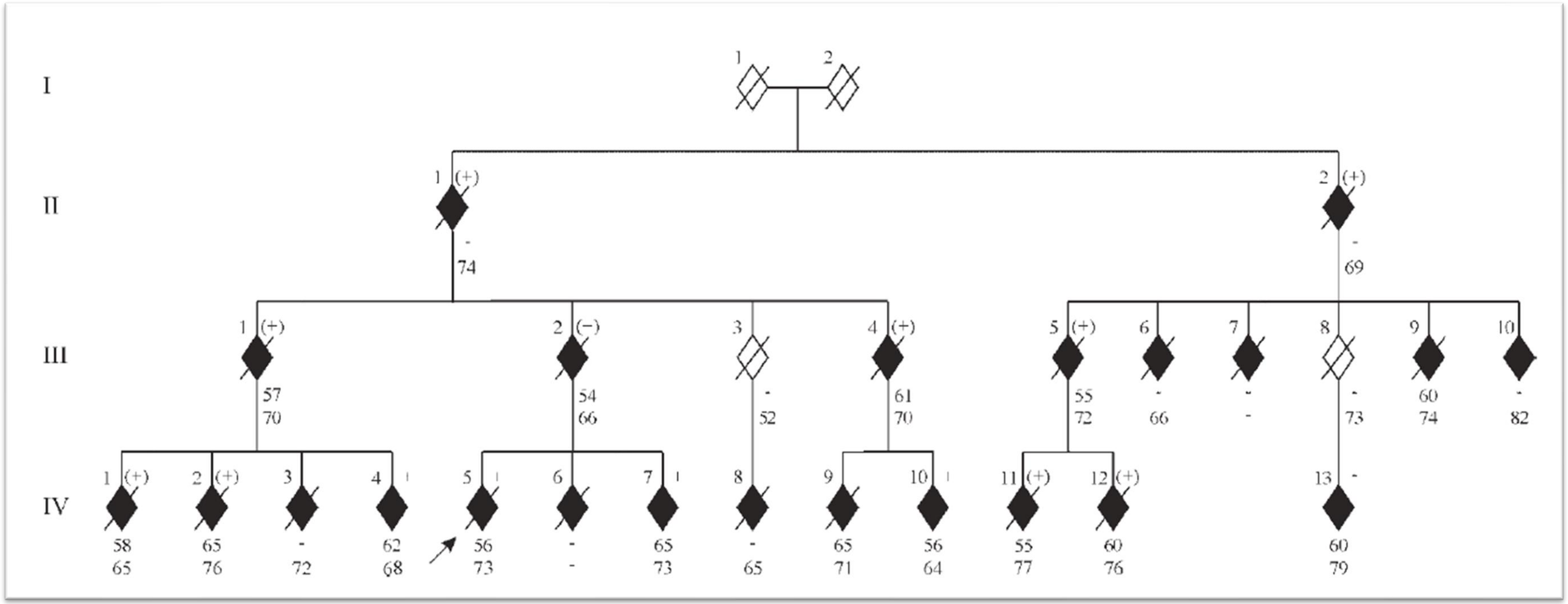
EARLY-ONSET DEMENTIA GENETICS



Rosa Rademakers

Christine Van Broeckhoven

1997 start PhD: “novel genes for early-onset dementia”, first project family AD/G, typical Alzheimer phenotype, negative for *APP*, *PSEN1*, *PSEN2*

→ MAPT p.(R406W), atypical form of “FTD”, clinically more similar to AD

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EARLY-ONSET DEMENTIA GENETICS

ORIGINAL RESEARCH ARTICLE

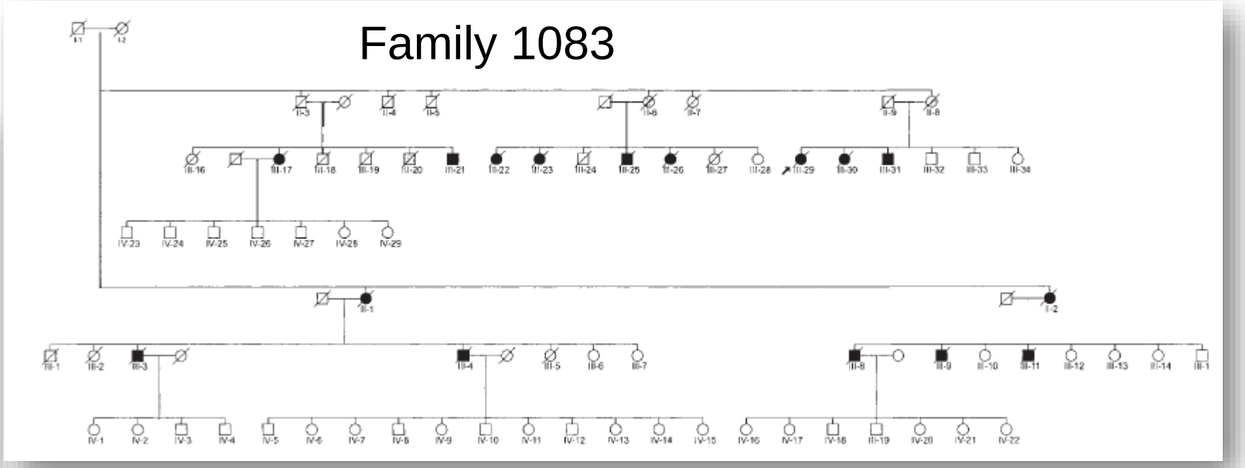
Tau negative frontal lobe dementia at 17q21: significant finemapping of the candidate region to a 4.8 cM interval

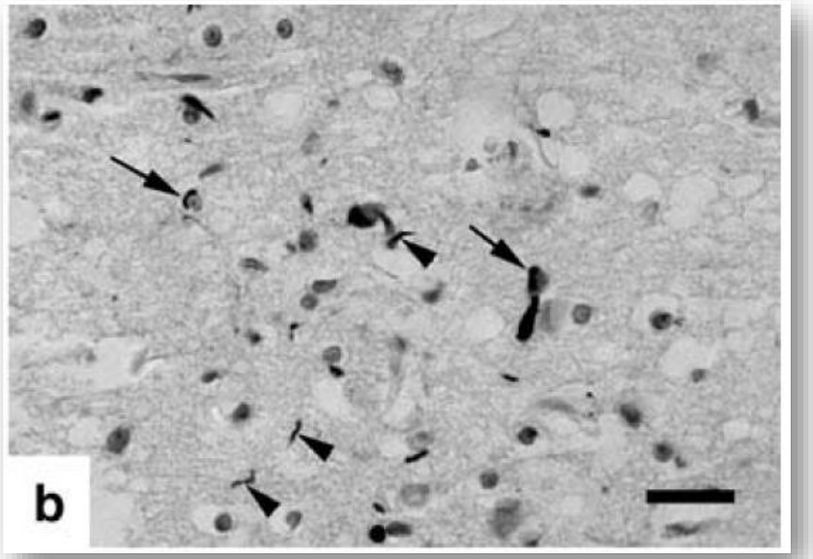
R Rademakers[1], M Cruts[1], B Dermaut[1], K Sleegers[2], SM Rosso[3], M Van den Broeck[1], H Backhovens[1], J van Swieten[3], CM van Duijn[1, 2] and C Van Broeckhoven[1]

[1]*Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology (VIB), University of Antwerp (UIA), Antwerpen, Belgium;* [2]*Department of Epidemiology & Biostatistics, Erasmus University Rotterdam, Rotterdam, The Netherlands;* [3]*Department of Neurology, University Hospital Rotterdam, Dijkzigt, Rotterdam, The Netherlands*

We report the results of a genome-wide search in a four-generation pedigree with autosomal dominant early-onset dementia (mean onset age: 64.9 years, range 53–79 years). In this family we previously excluded the known Alzheimer's disease genes based on linkage analysis and mutation screening of the amyloid precursor protein gene (exons 16 and 17) and the presenilin 1 and 2 genes. In addition we excluded mutations in the prion protein gene and exons 9–13 of the microtubule associated protein tau (*MAPT*) gene. We obtained conclusive linkage with chromosome 17q21 markers with a maximum multi-point LOD score of 5.51 at D17S951 and identified a candidate region of 4.8 cM between D17S1787 and D17S958 containing *MAPT*. Recent clinical and neuropathological follow-up of the family showed that the phenotype most closely resembled frontotemporal dementia (FTD) characterized by dense ubiquitin-positive neuronal inclusions that were tau negative. Extensive mutation analysis of *MAPT* identified 38 sequence variations in exons, introns, untranslated regions and the 5′ regulatory sequence, however none was comprised within the disease haplotype. Although our findings do not entirely exclude a mutation in a yet unanalyzed region of *MAPT*, the apparent absence of *MAPT* mutations combined with the lack of tau pathology is highly suggestive for another defective gene at 17q21 responsible for FTD in this family.

Molecular Psychiatry (2002) **7,** 1064–1074. doi:10.1038/sj.mp.4001198





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EARLY-ONSET DEMENTIA GENETICS

A Belgian ancestral haplotype harbours a highly prevalent mutation for 17q21-linked tau-negative FTLD

Brain (2006), **129**, 841–852

Julie van der Zee,[1] Rosa Rademakers,[1] Sebastiaan Engelborghs,[2,6] Ilse Gijselinck,[1] Veerle Bogaerts,[1] Rik Vandenberghe,[5] Patrick Santens,[4] Jo Caekebeke,[7] Tim De Pooter,[1] Karin Peeters,[1] Ursula Lübke,[3] Marleen Van den Broeck,[1] Jean-Jacques Martin,[3] Marc Cruts,[1] Peter P. De Deyn,[2,6] Christine Van Broeckhoven[1] and Bart Dermaut[1,4]

[1]Neurodegenerative Brain Diseases Group, Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, [2]Laboratory of Neurochemistry and Behavior, [3]Laboratory of Neuropathology, Institute Born-Bunge, University of Antwerp, [4]Department of Neurology, Ghent University Hospital, University of Ghent, [5]Department of Neurology, University Hospital Gasthuisberg, Catholic University of Leuven, [6]Department of Neurology and Memory Clinic, Middelheim General Hospital, Antwerp and [7]Department of Neurology, OLV Hospital Aalst, Belgium

Correspondence to: Prof. Dr Christine Van Broeckhoven, Neurodegenerative Brain Diseases Group, VIB8 Department of Molecular Genetics, University of Antwerp, Building V, Room 0.10, Universiteitsplein 1, BE-2610 Antwerpen, Belgium
E-mail: christine.vanbroeckhoven@ua.ac.be

Among patients with frontotemporal lobar degeneration (FTLD), the respective frequencies of dominant 17q21-linked tau-negative FTLD (with unidentified molecular defect) and 17q21-linked tau-positive FTLD (due to *MAPT* mutations) remain unknown. Here, in a series of 98 genealogically unrelated Belgian FTLD patients, we identified an ancestral 8 cM *MAPT* containing haplotype in two patients belonging to multiplex families DR2 and DR8, without demonstrable *MAPT* mutations, in which FTLD was conclusively linked to 17q21 [maximum summed log of the odds (LOD) score of 5.28 at D17S931]. Interestingly, the same DR2–DR8 ancestral haplotype was observed in five additional familial FTLD patients, indicative of a founder effect. In the FTLD series, the DR2–DR8 ancestral haplotype explained 7% (7 out of 98) of FTLD and 17% (7 out of 42) of familial FTLD and was seven times more frequent than *MAPT* mutations (1 out of 98 or 1%). Clinically, DR2–DR8 haplotype carriers presented with FTLD often characterized by language impairment, and in one carrier the neuropathological diagnosis was FTLD with rare tau-negative ubiquitin-positive inclusions. Together, these results strongly suggest that the DR2–DR8 founder haplotype at 17q21 harbours a tau-negative FTLD causing mutation that is a much more frequent cause of FTLD in Belgium than *MAPT* mutations.

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EARLY-ONSET DEMENTIA GENETICS

A Belgian ancestral haplotype harbours a highly prevalent mutation for 17q21-linked tau-negative FTLD

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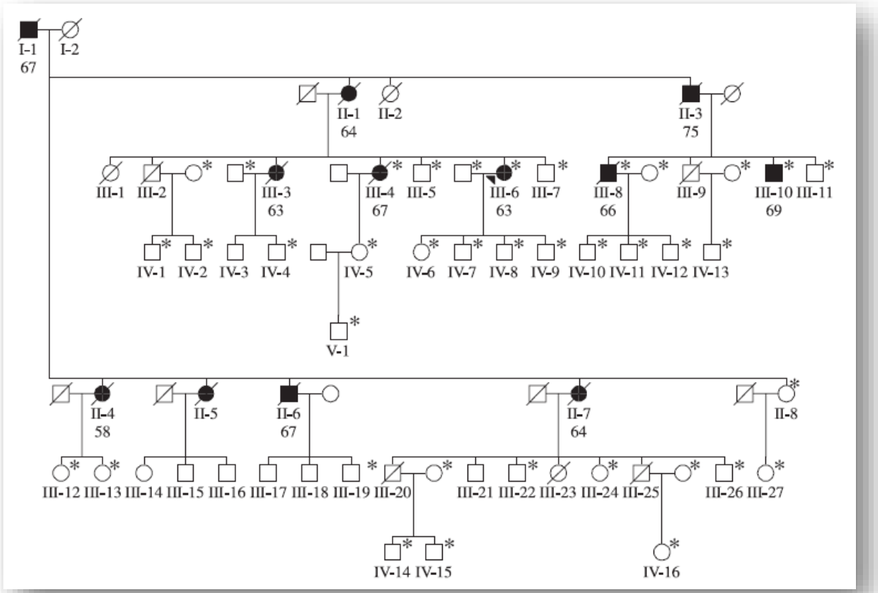
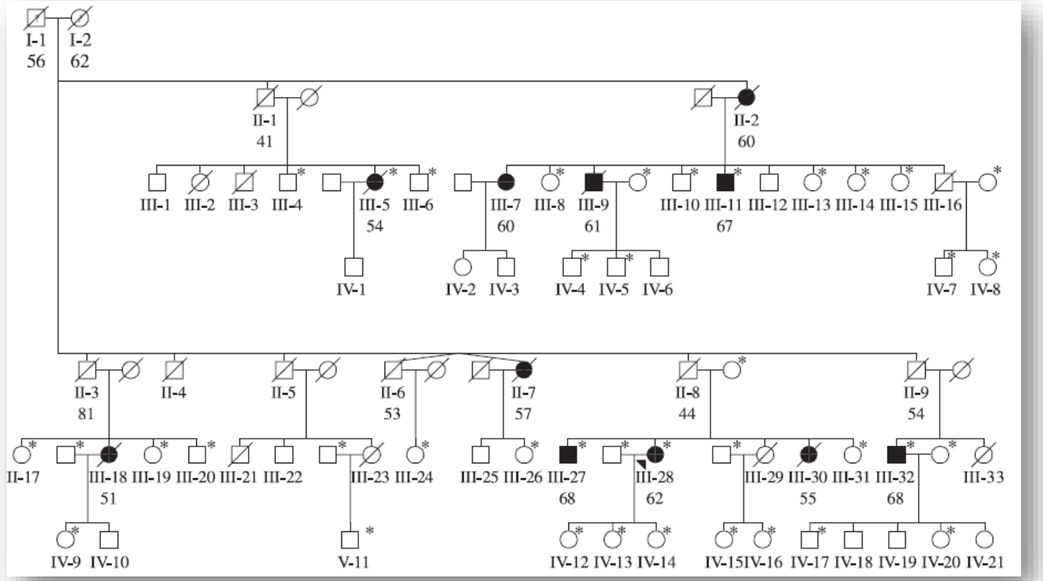
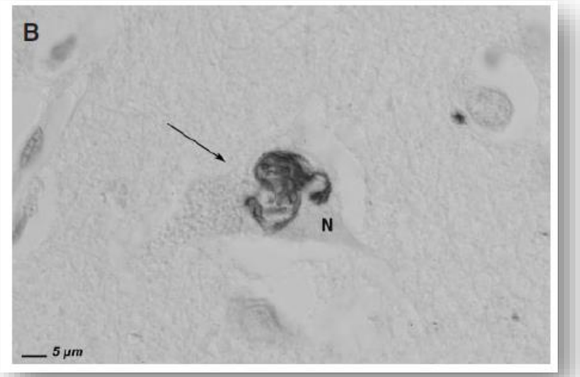
Family DR2



Family DR8





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EARLY-ONSET DEMENTIA GENETICS

nature Vol 442|24 August 2006|doi:10.1038/nature05017

LETTERS

Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21

Marc Cruts[1,2,5], Ilse Gijselinck[1,2,5], Julie van der Zee[1,2,5], Sebastiaan Engelborghs[3,5,6], Hans Wils[1,2,5], Daniel Pirici[1,2,5], Rosa Rademakers[1,2,5], Rik Vandenberghe[7], Bart Dermaut[9], Jean-Jacques Martin[4,5], Cornelia van Duijn[10], Karin Peeters[1,2,5], Raf Sciot[8], Patrick Santens[9], Tim De Pooter[1,2,5], Maria Mattheijssens[1,2,5], Marleen Van den Broeck[1,2,5], Ivy Cuijt[1,2,5], Krist'l Vennekens[1,2,5], Peter P. De Deyn[3,5,6], Samir Kumar-Singh[1,2,5] & Christine Van Broeckhoven[1,2,5]

nature Vol 442|24 August 2006|doi:10.1038/nature05016

LETTERS

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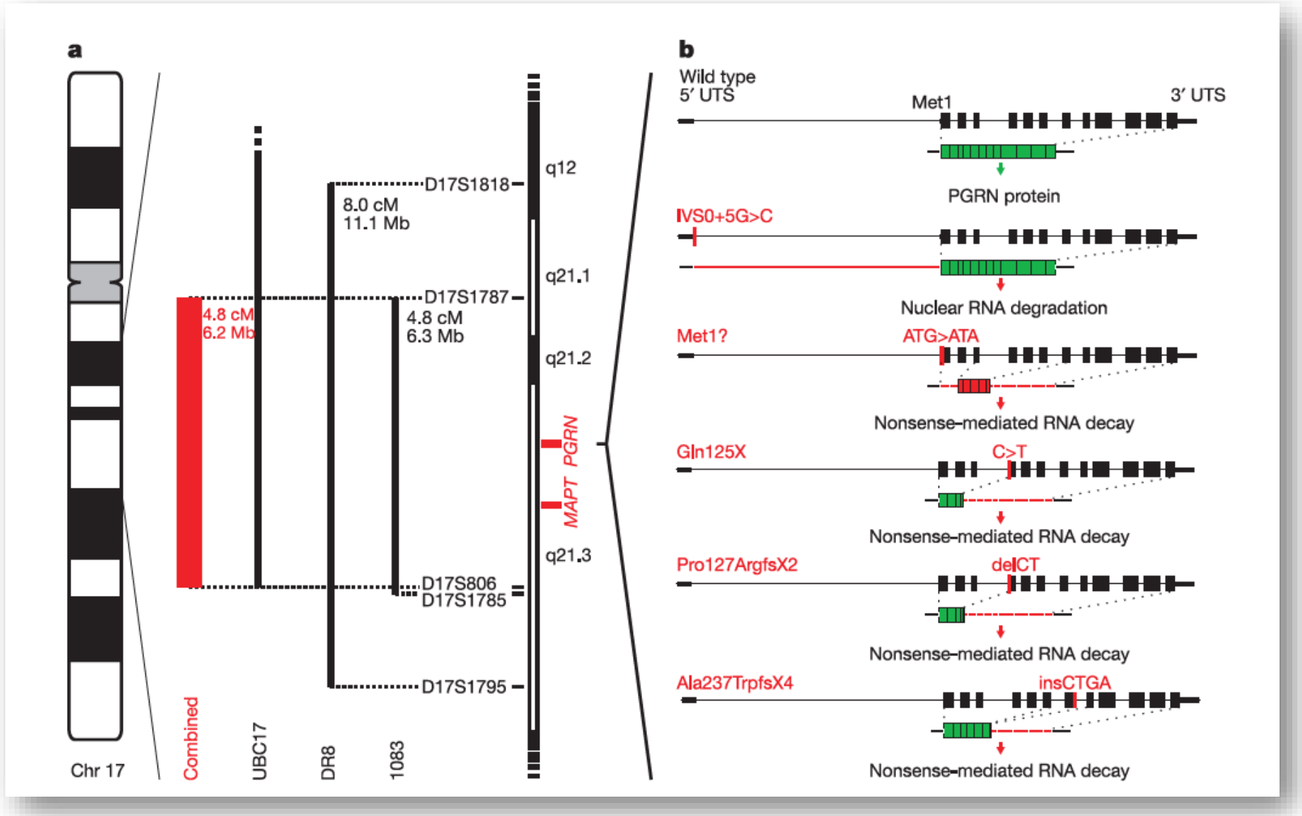

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Trends in Pharmacological Sciences, August 2022, Vol. 43, No. 8

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Review

Progranulin as a therapeutic target in neurodegenerative diseases

Herve Rhinn,[1] Nadine Tatton,[1] Stella McCaughey,[1] Michael Kurnellas,[1] and Arnon Rosenthal[1,*]

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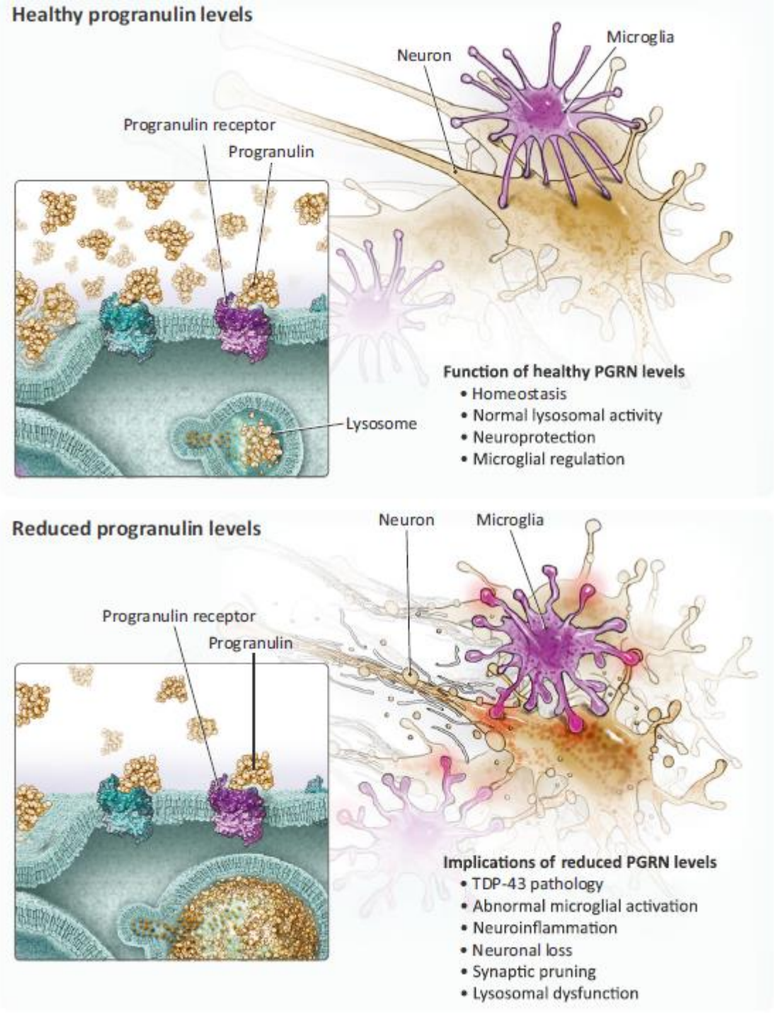

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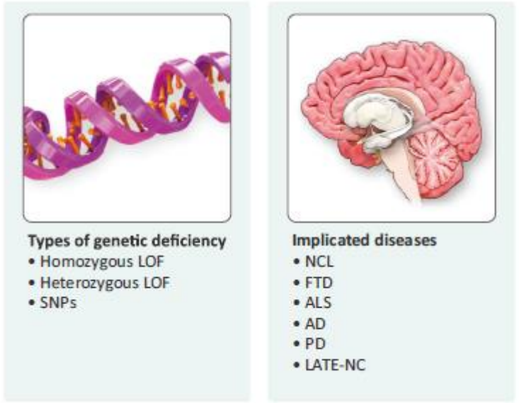

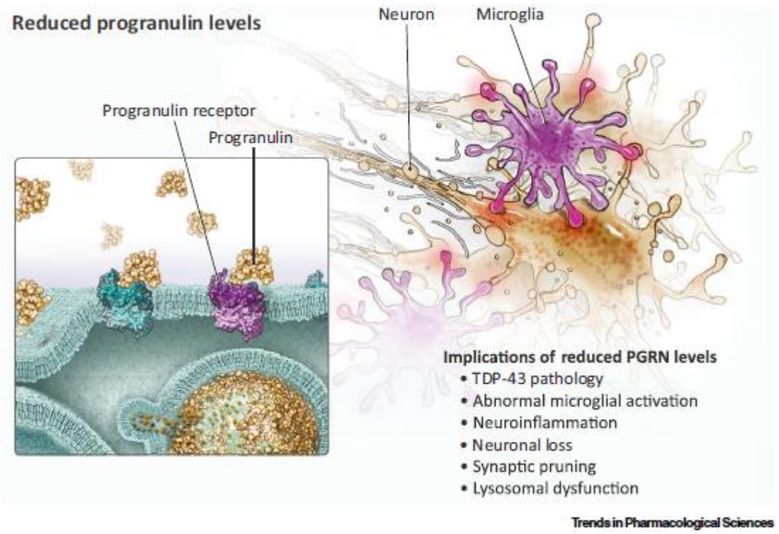

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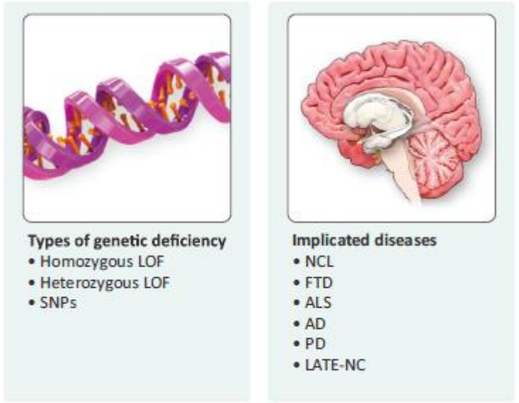

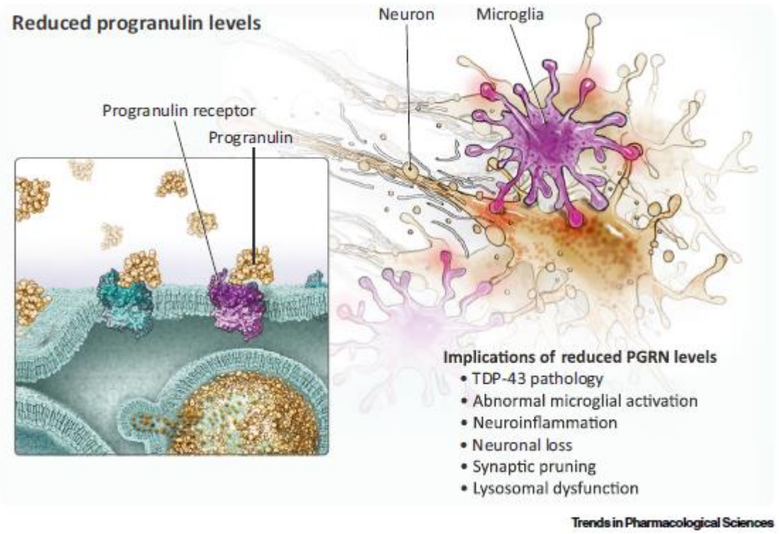

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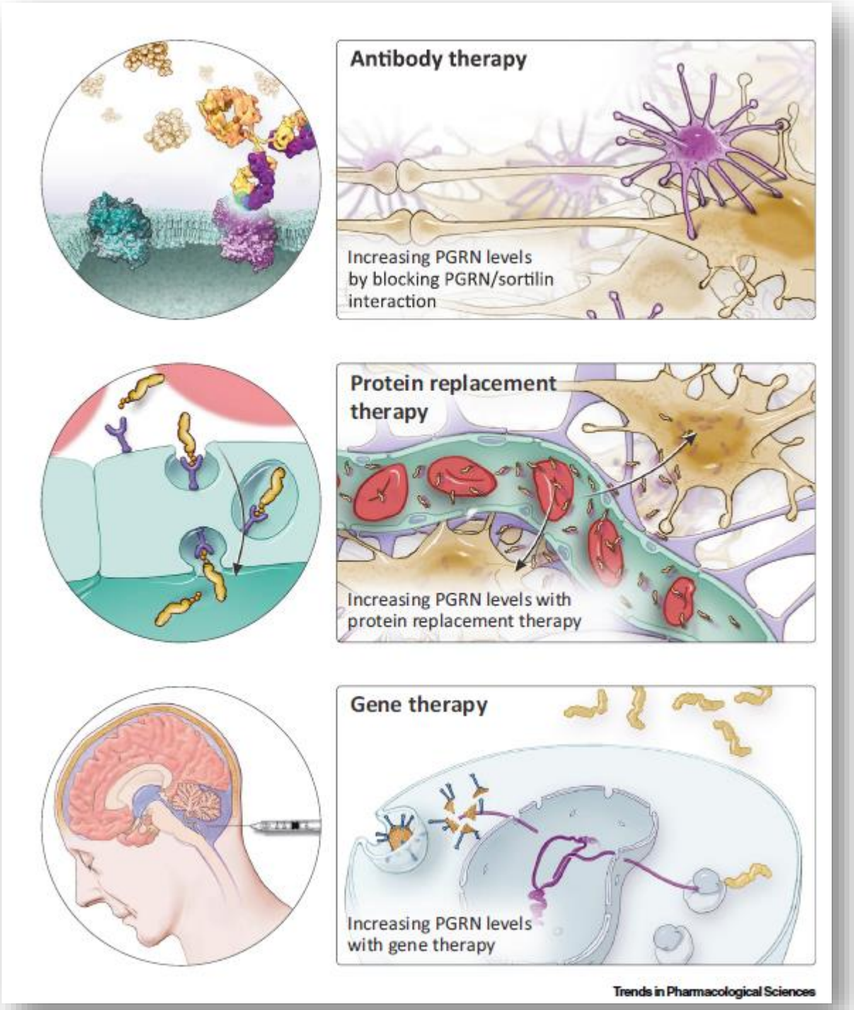

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Herve Rhinn,[1] Nadine Tatton,[1] Stella McCaughey,[1] Michael Kurnellas,[1] and Arnon Rosenthal [1,*]

INTERIM BIOMARKER DATA FROM A FIRST-IN-HUMAN GENE THERAPY CLINICAL TRIAL FOR FRONTOTEMPORAL DEMENTIA PATIENTS (FTD) WITH GRN MUTATION (PROCLAIM TRIAL).

Presenter Uspenskaya Olga (France)
Lecture Time 14:50 - 15:05

Abstract

RESCUE OF FTLD-ASSOCIATED TDP-43 PATHOLOGY AND NEURODEGENERATION BY PERIPHERAL AAV-MEDIATED EXPRESSION OF BRAIN-PENETRANT PROGRANULIN

Presenter Marvin Reich (Germany)
Lecture Time 15:05 - 15:20

Abstract

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