New Approaches towards Interventions in Frontotemporal Dementia

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New Approaches towards Interventions in Alzheimer's Dementia: Focus Efforts on Curing FTD!

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World War AD!

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World War AD!

- ~40 million people live with dementia
  - expected to double by 2030
  - triple by 2050

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http://www.who.int/mediacentre/news/releases/2012/dementia_20120411/en/

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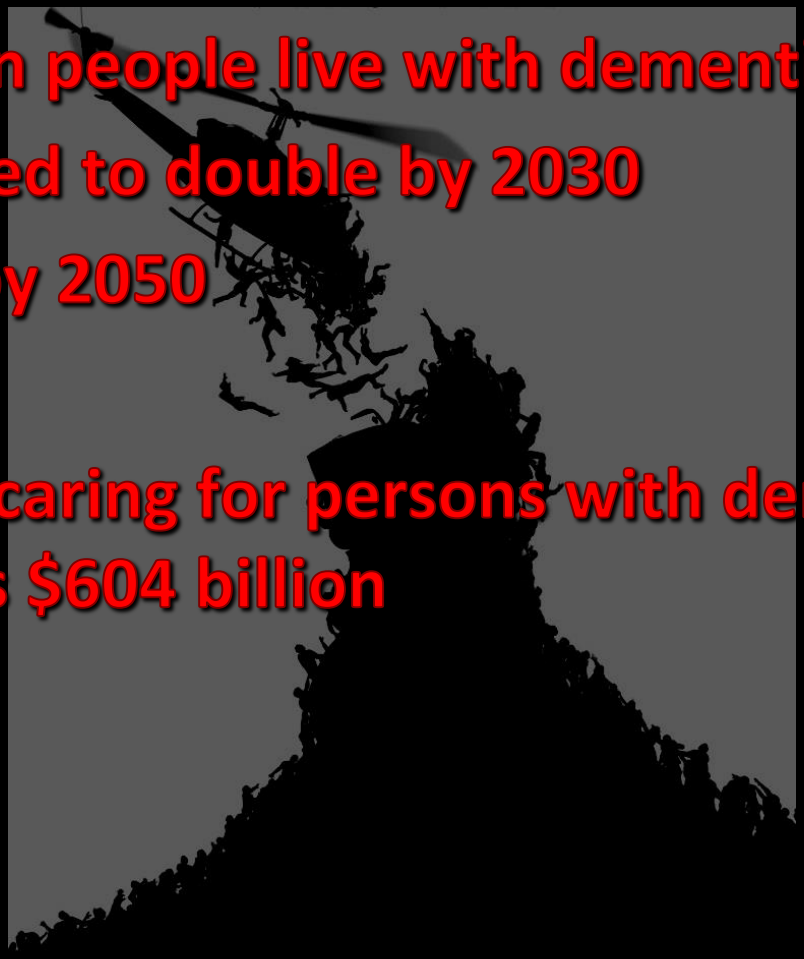
  - triple by 2050

- Currently caring for persons with dementia world wide costs $604 billion



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World War AD!

- ~40 million people live with dementia
  - expected to double by 2030
  - triple by 2050
- Currently caring for persons with dementia world wide costs $604 billion
- 70% of these dementia cases are thought to have AD!

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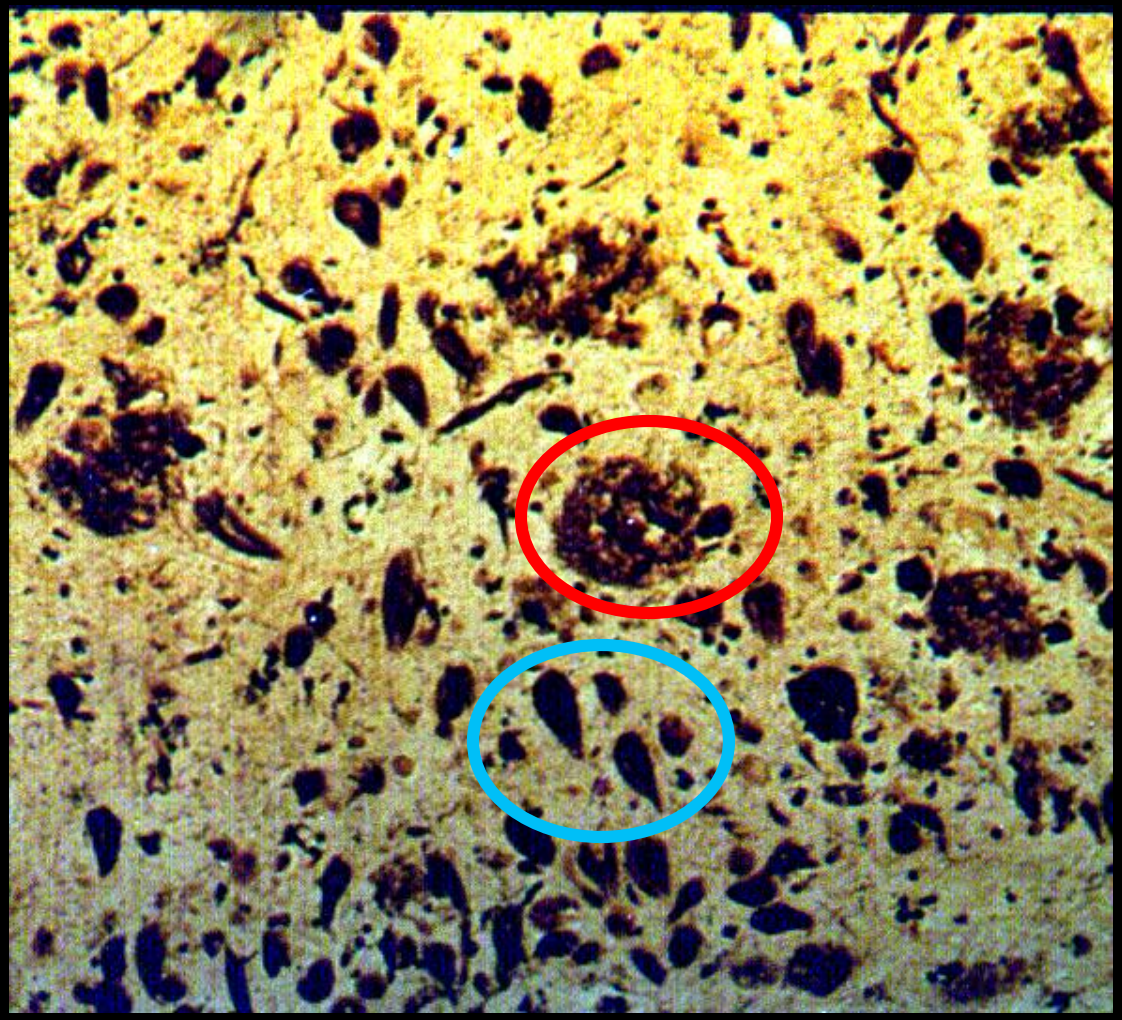
Alzheimer's Disease

Amyloid plaques

- Extra-cellular
- Amyloid-β (Aβ)

Neurofibrillary tangles

- Intra-cellular
- Tau



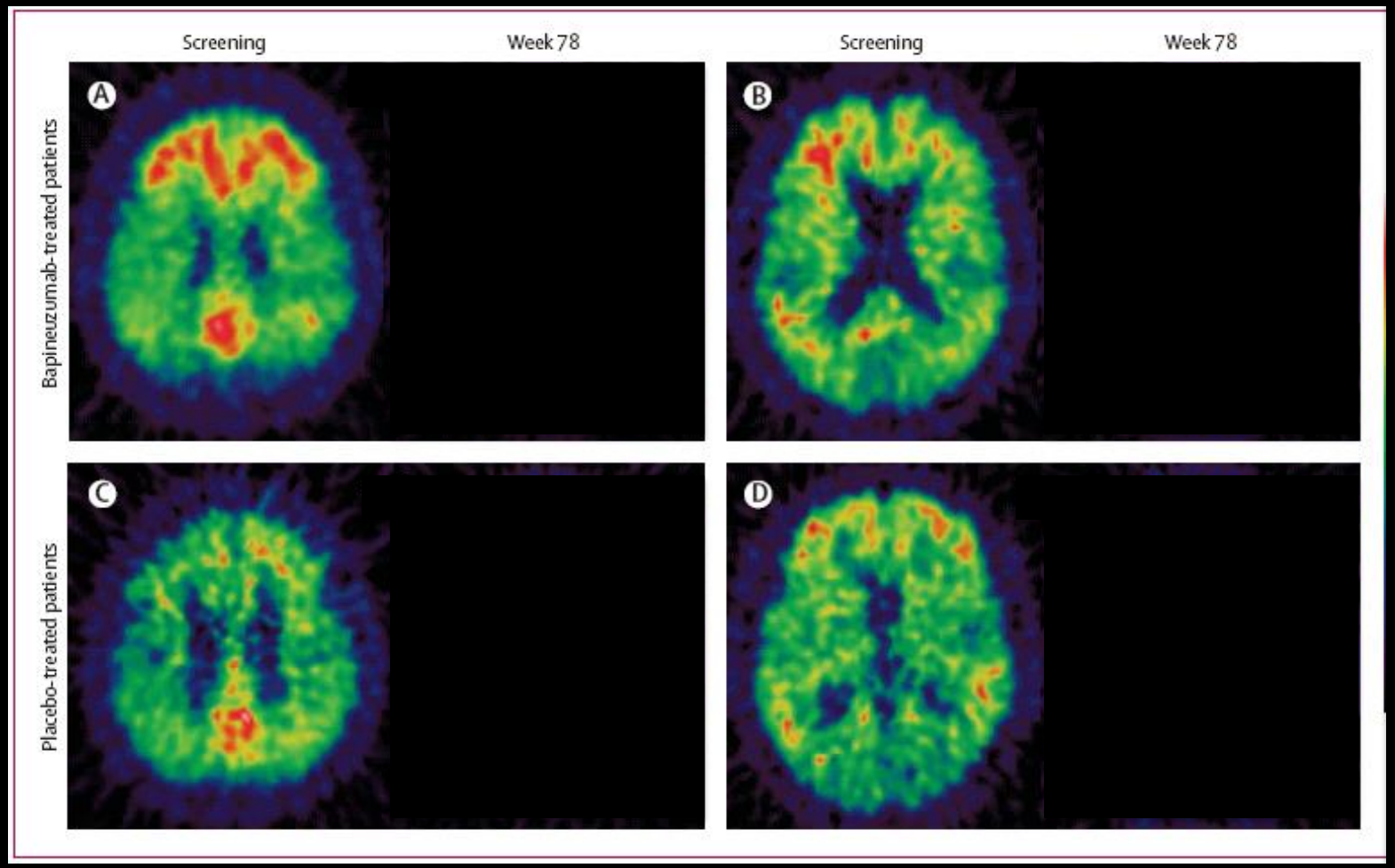
Amyloid Hypothesis

- Mutations in Amyloid Precursor Protein (APP) or APP processing genes cause AD in humans and animal models
  - Extra copy of APP gene on Chromosome 21 in Down's syndrome causes AD
  - Rare variant in APP *protects* against AD
- Risk modifying genes for sporadic AD are involved in the amyloid cascade (ApoE)
- Aβ aggregates are toxic to synapses, neurons, & glia

Anti-Aβ Monoclonal Antibodies

Bap

Pbo



Rinne et al., *Lancet Neurology* 2010

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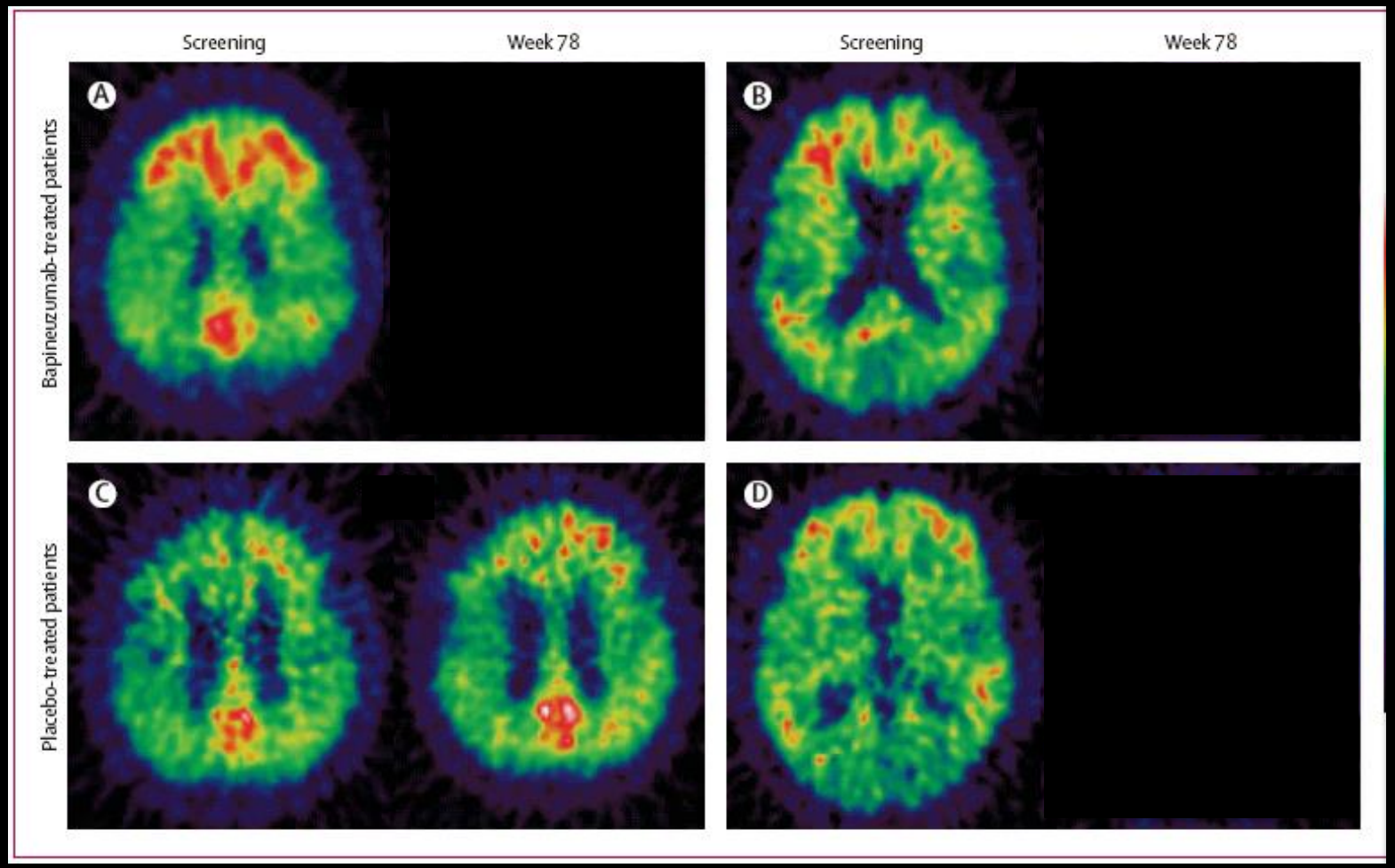

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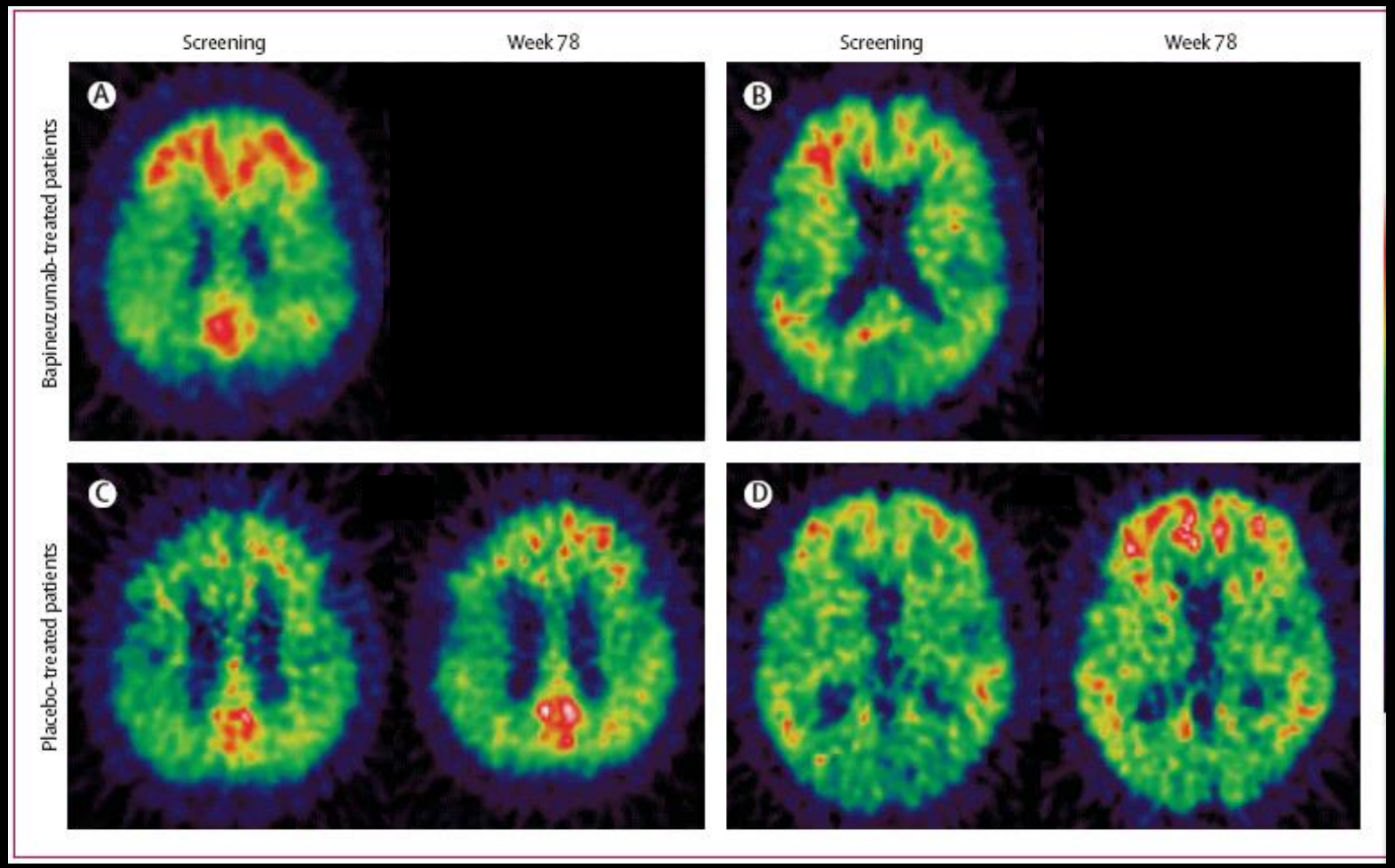

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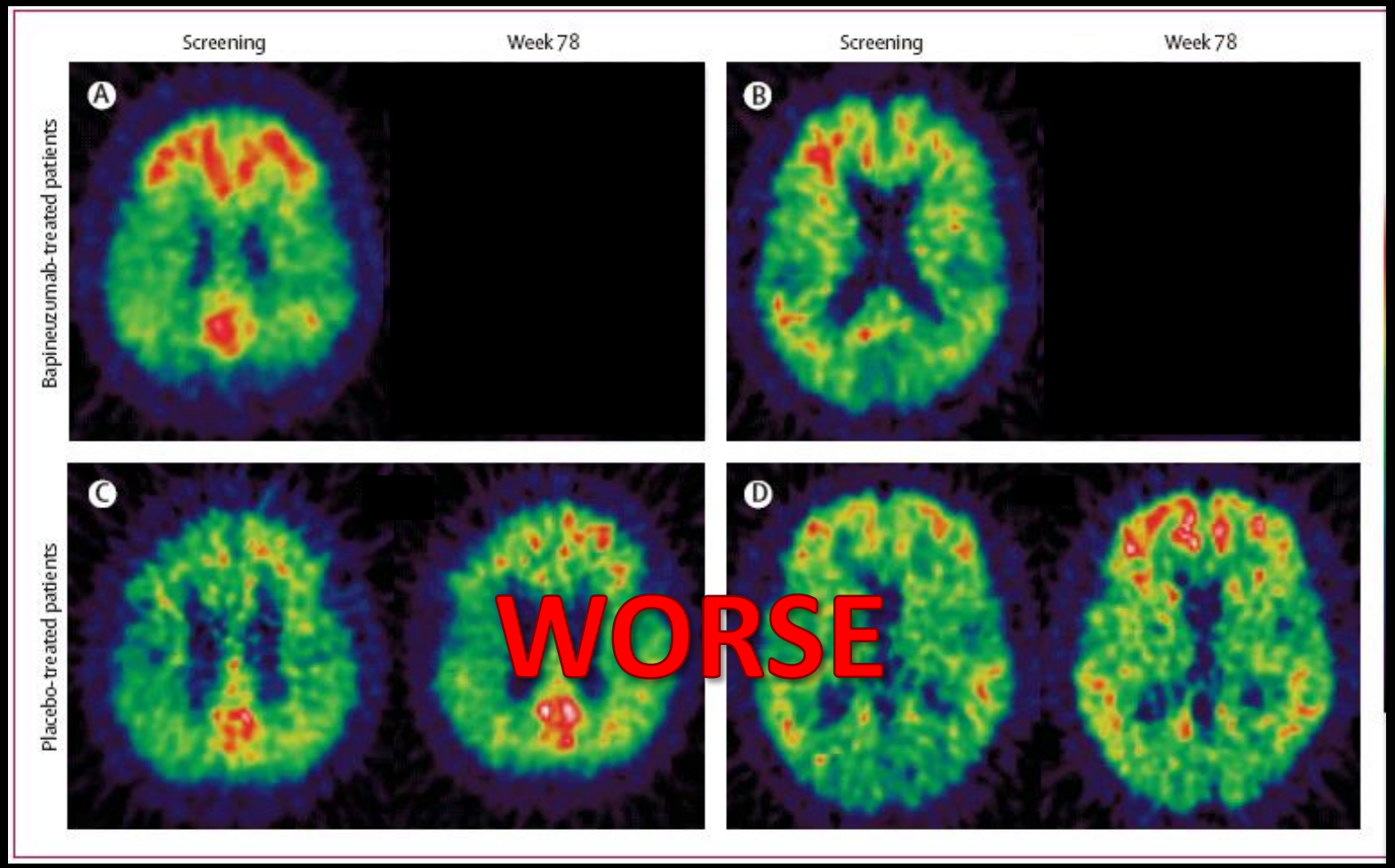

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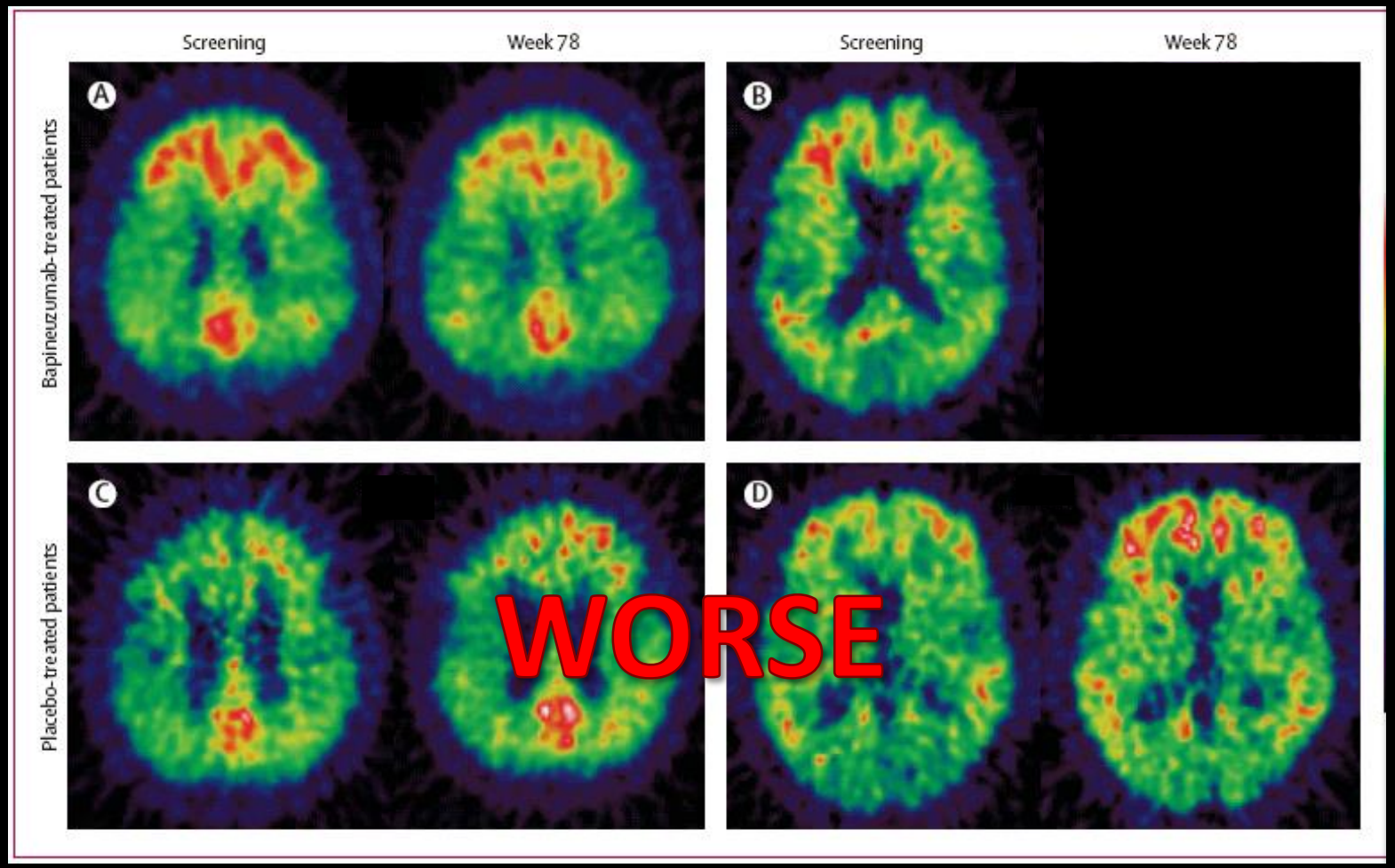

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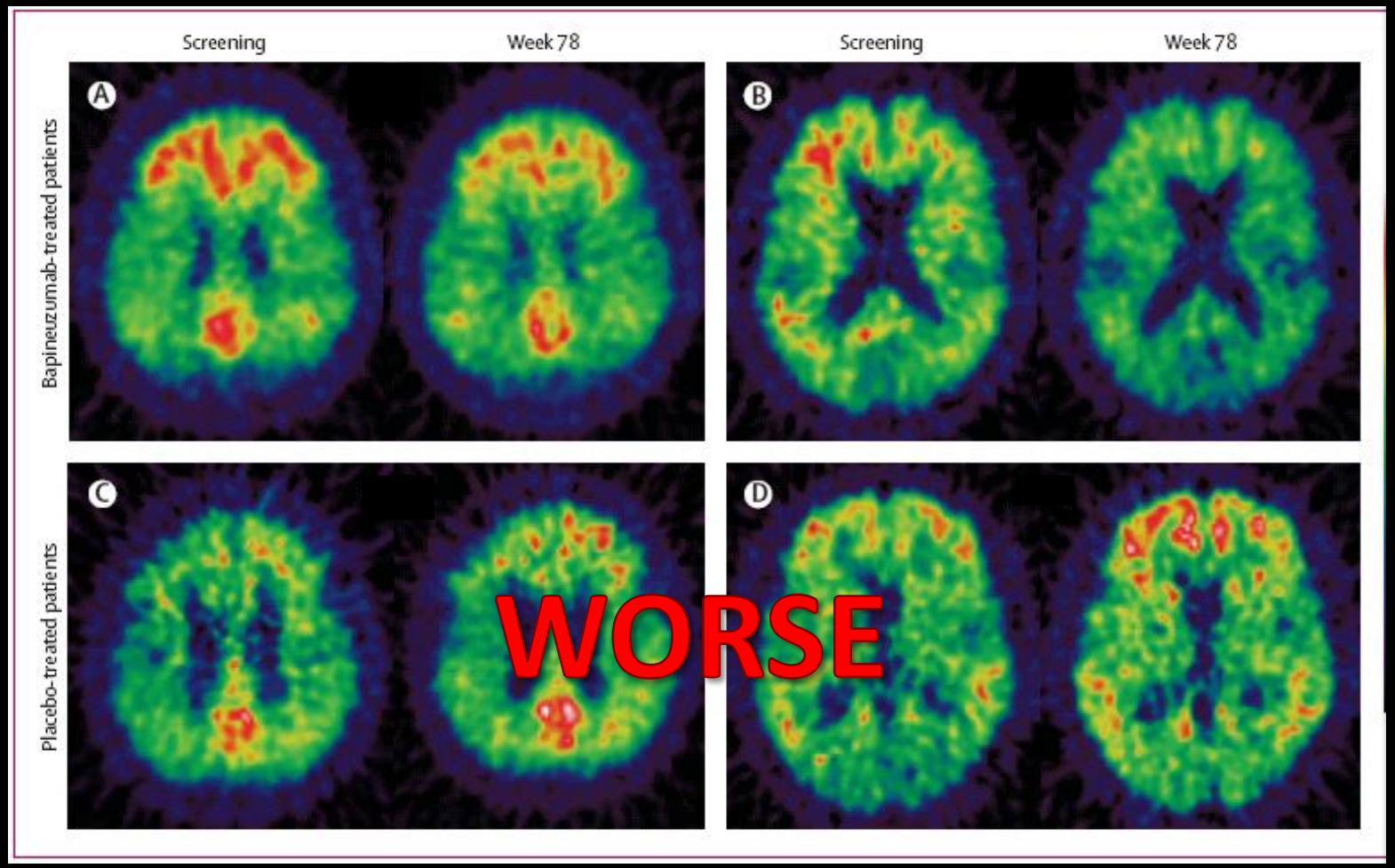

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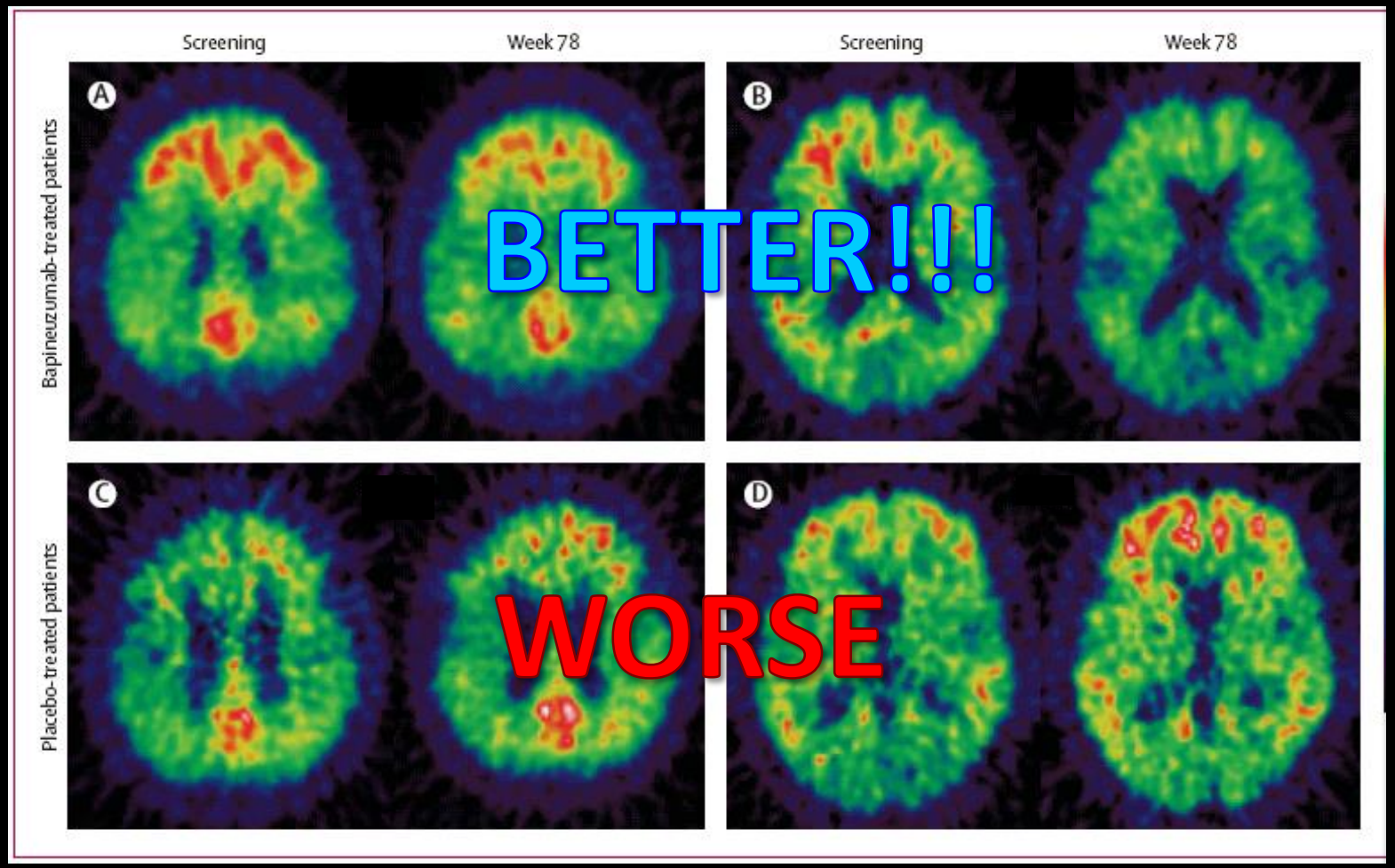

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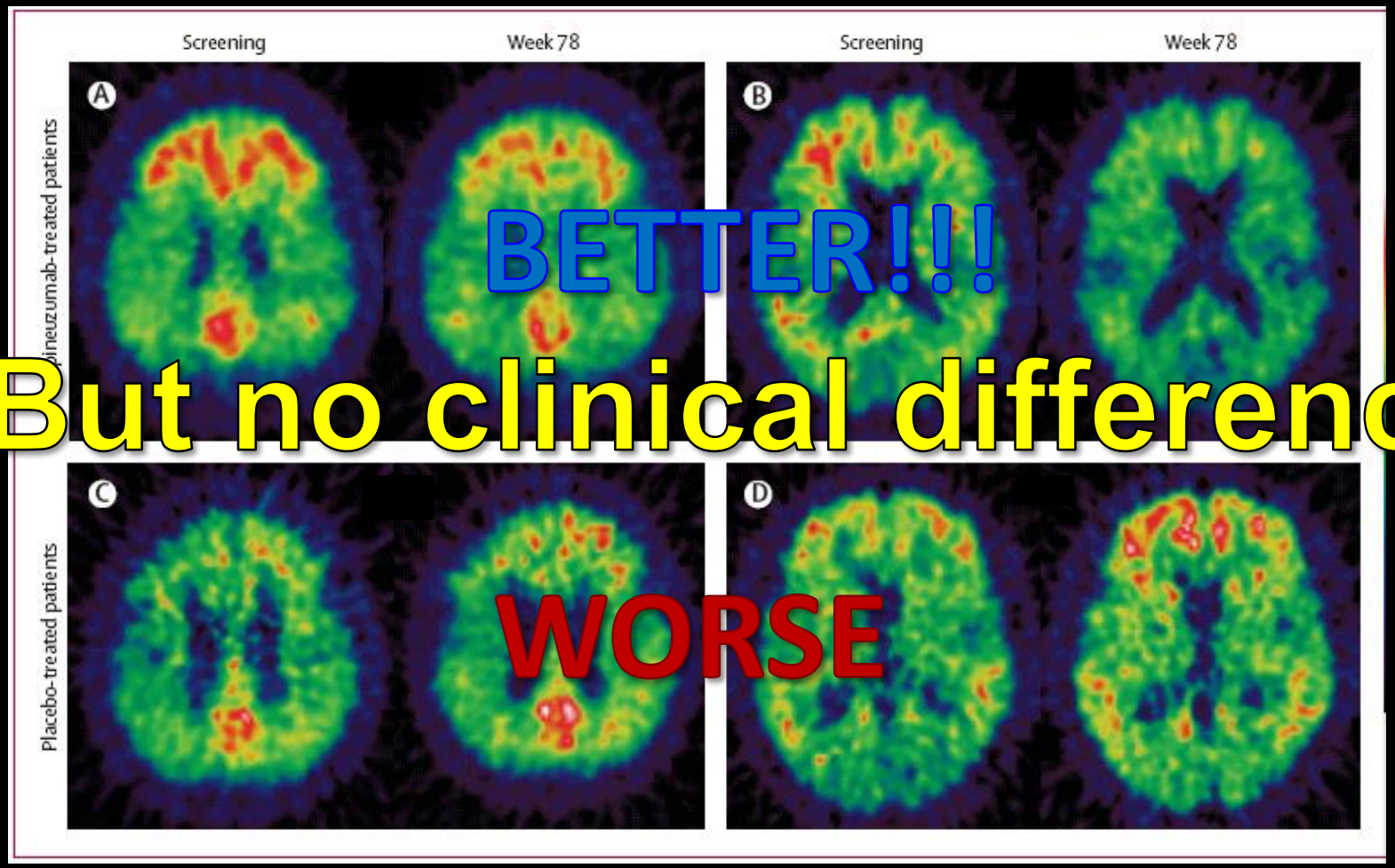

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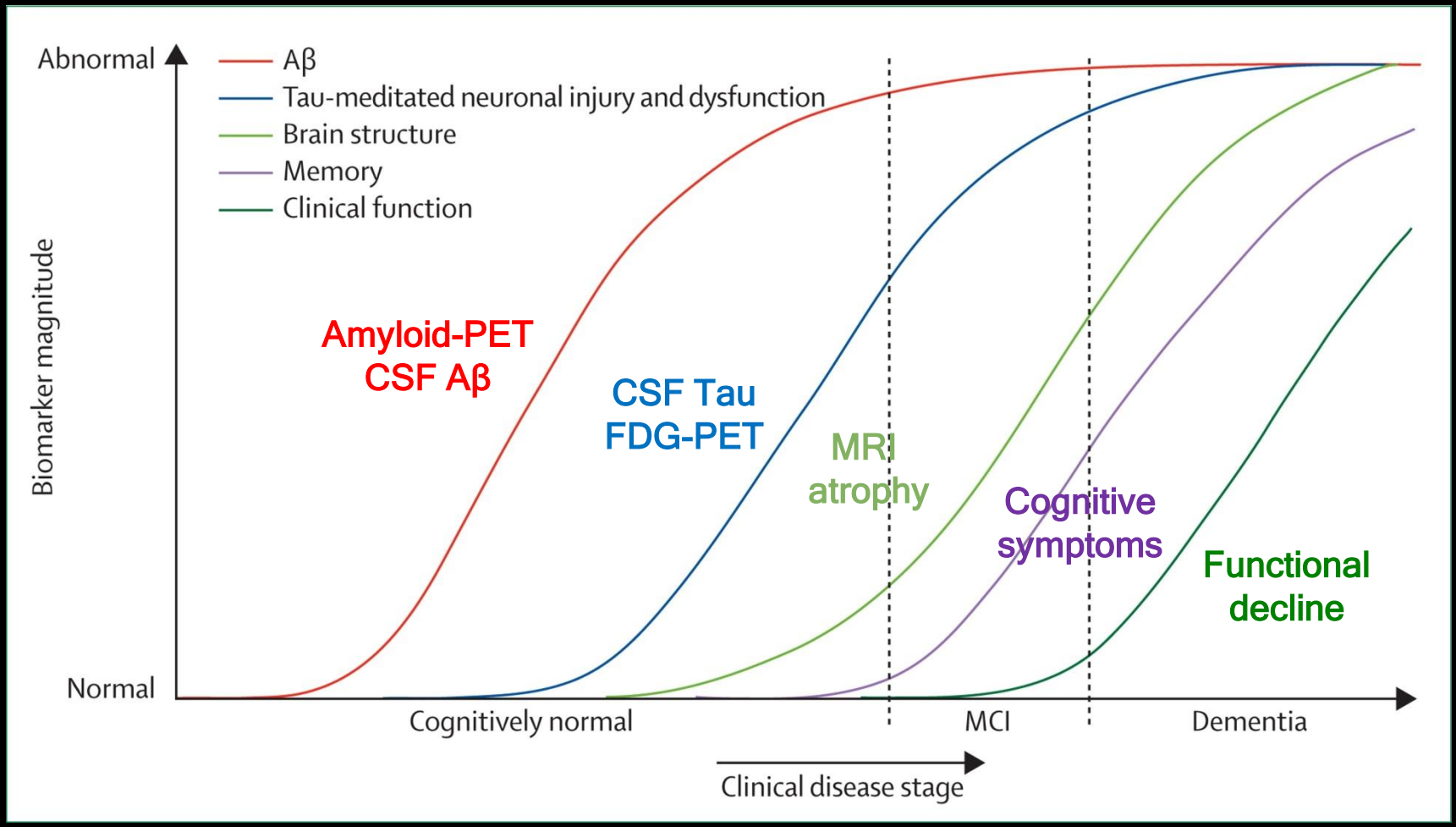
Failure of Amyloid Therapies:



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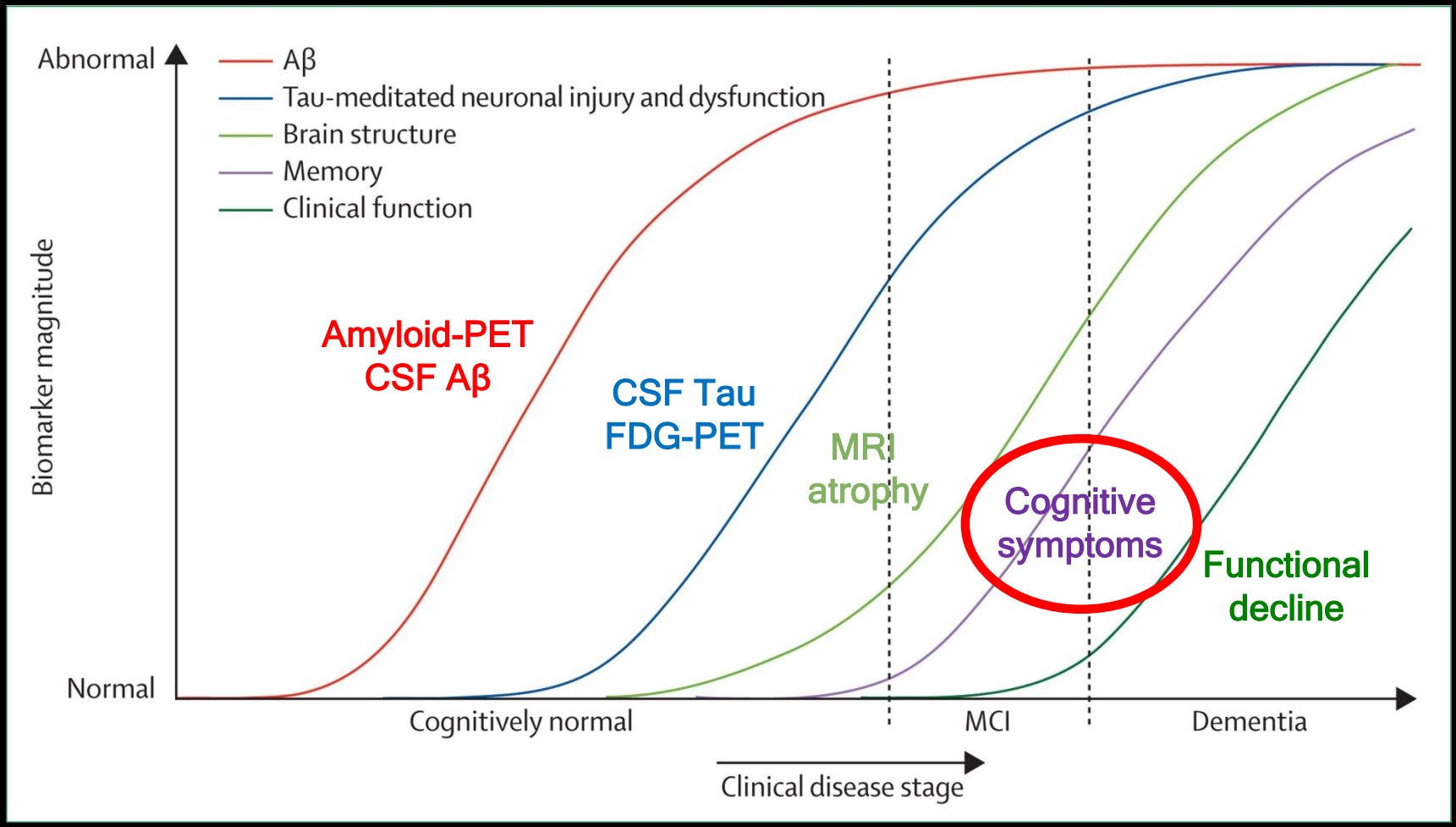

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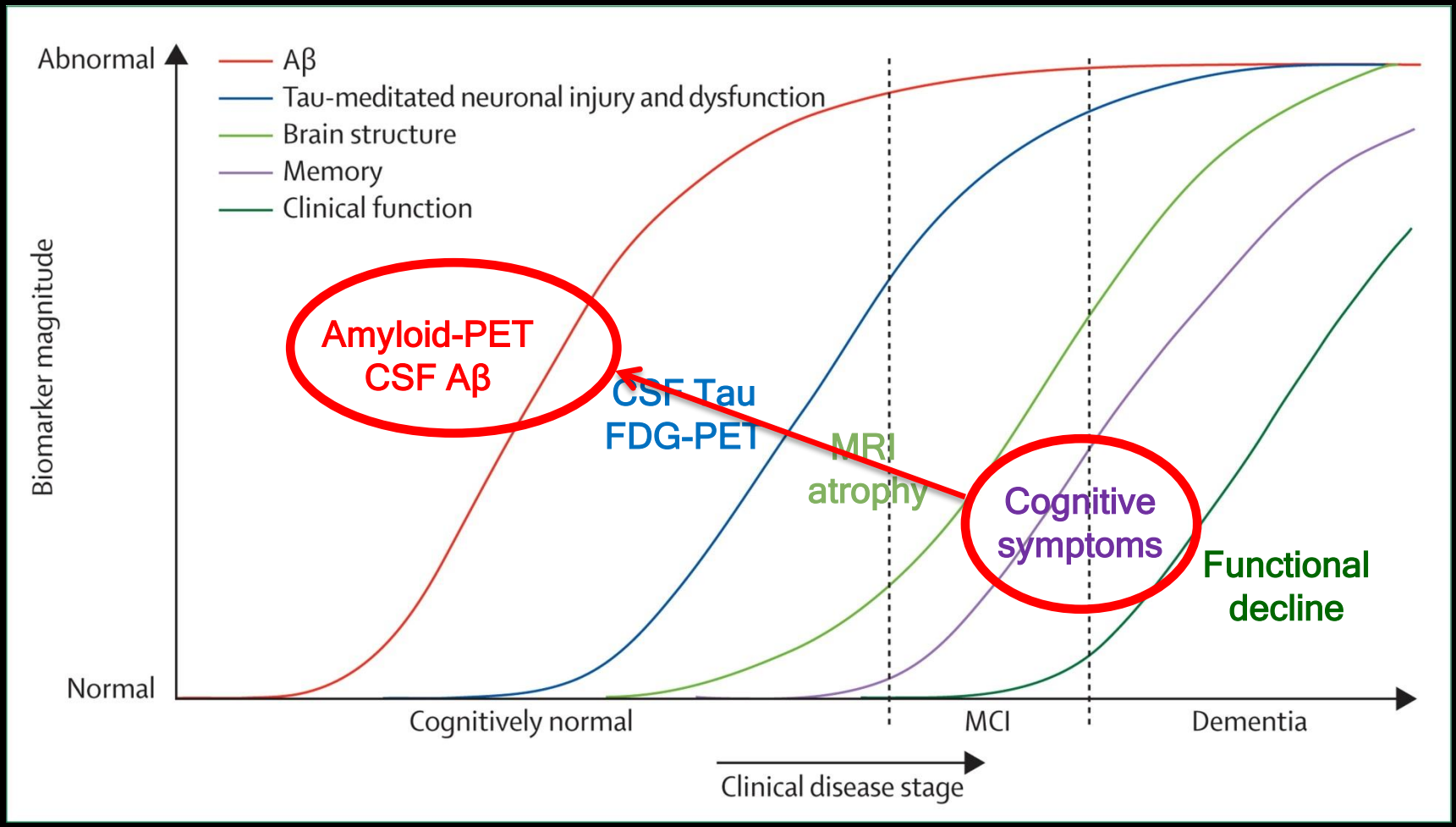
Failure of Amyloid Therapies: Too Late?



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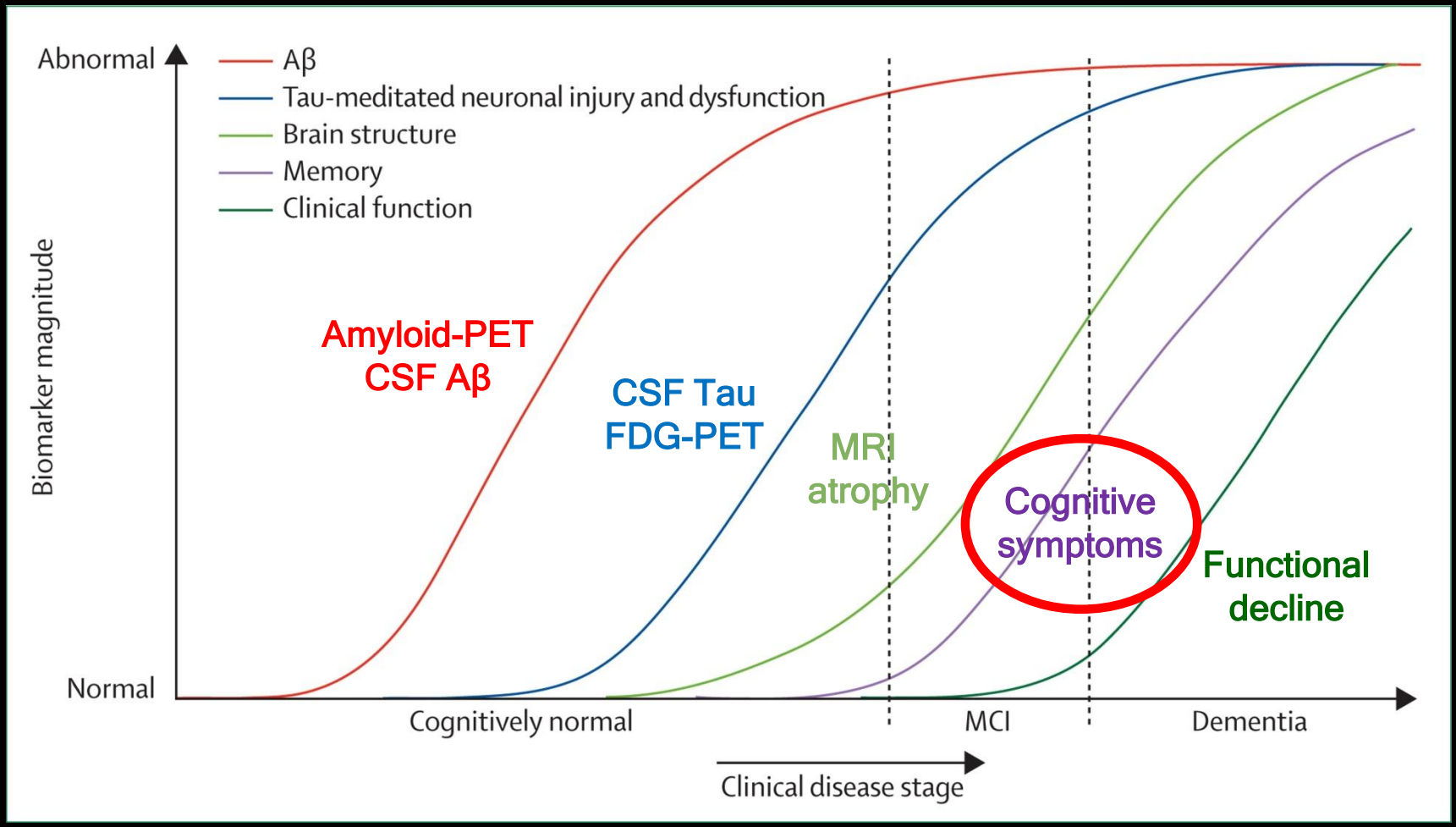
Failure of Amyloid Therapies: Too Late?

- Dominantly Inherited Alzheimer's Network (DIAN), Alzheimer's Prevention Initiative (API)
  - Registry of AD mutation carriers for longitudinal biomarker studies and preventive trials
  - First trial (crenezumab)

- Anti-Amyloid treatment in Asymptomatic AD (A4)
  - Asymptomatic individuals over age 70 with positive amyloid PET
  - First trial (solanezumab)

Failure of Amyloid Therapies:



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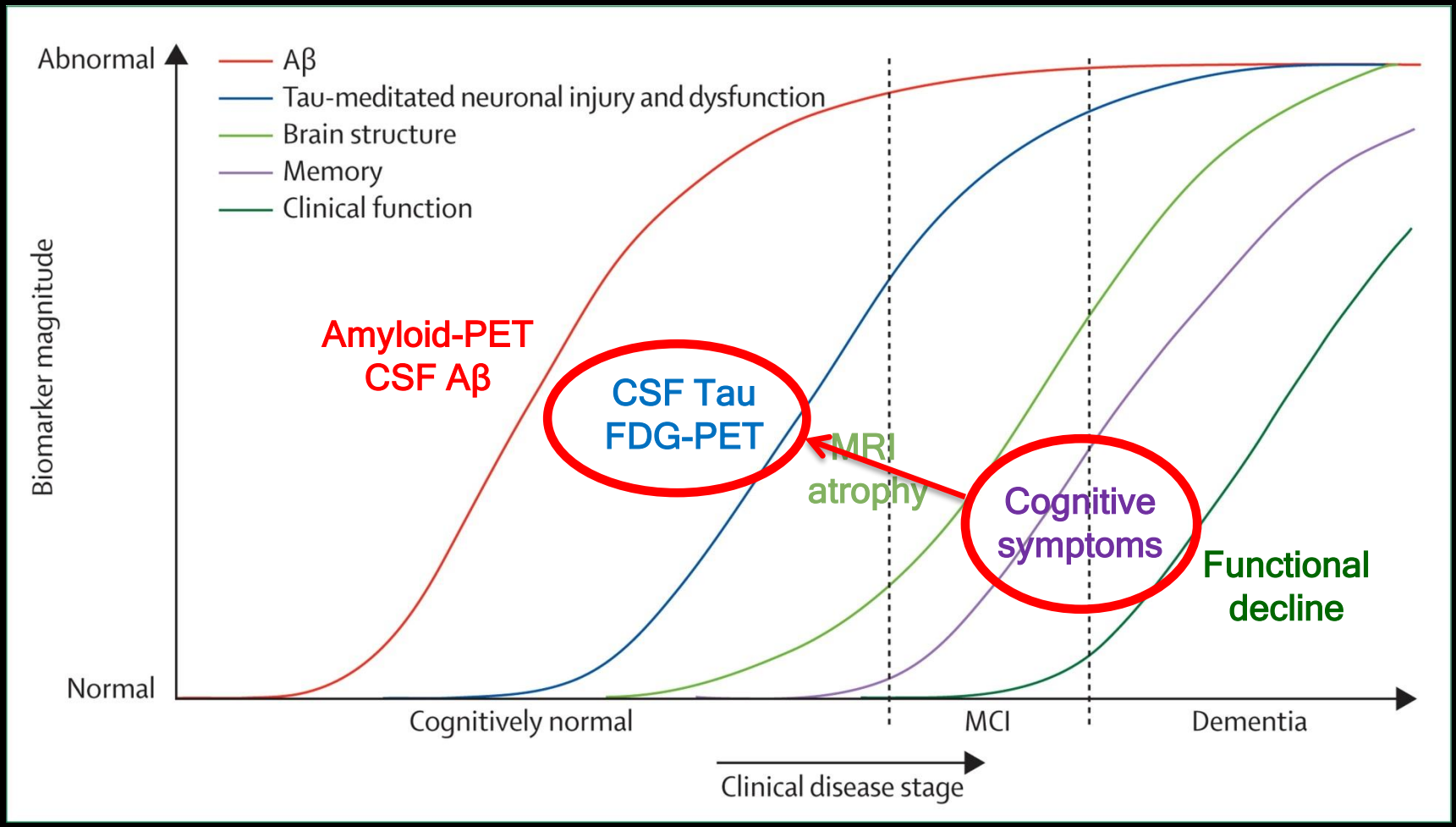
Failure of Amyloid Therapies: Wrong Target?



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Support for Tau Hypothesis

- Tau is important for microtubule health

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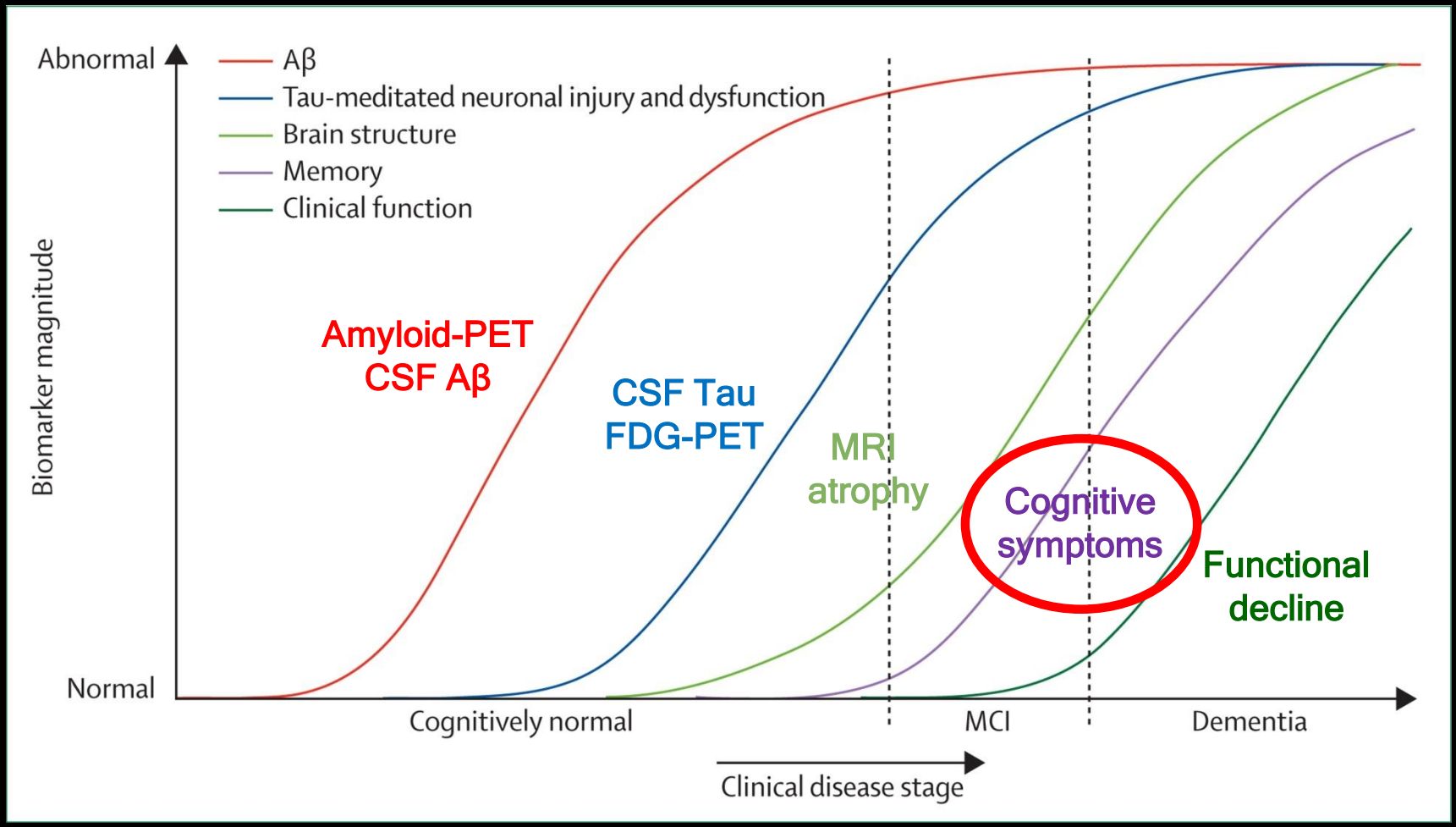
- Clinical symptoms in AD correlate better with tau tangles than amyloid plaques
- Knocking out tau in AD mouse model ameliorates behavioral deficits
- Aggregates are toxic, and… infectious!?!

Tau as a Prion

- Strains of tau spread from one cell to next
- Moving along specific circuits
- Can be removed by monoclonal antibodies

Failure of Amyloid Therapies:



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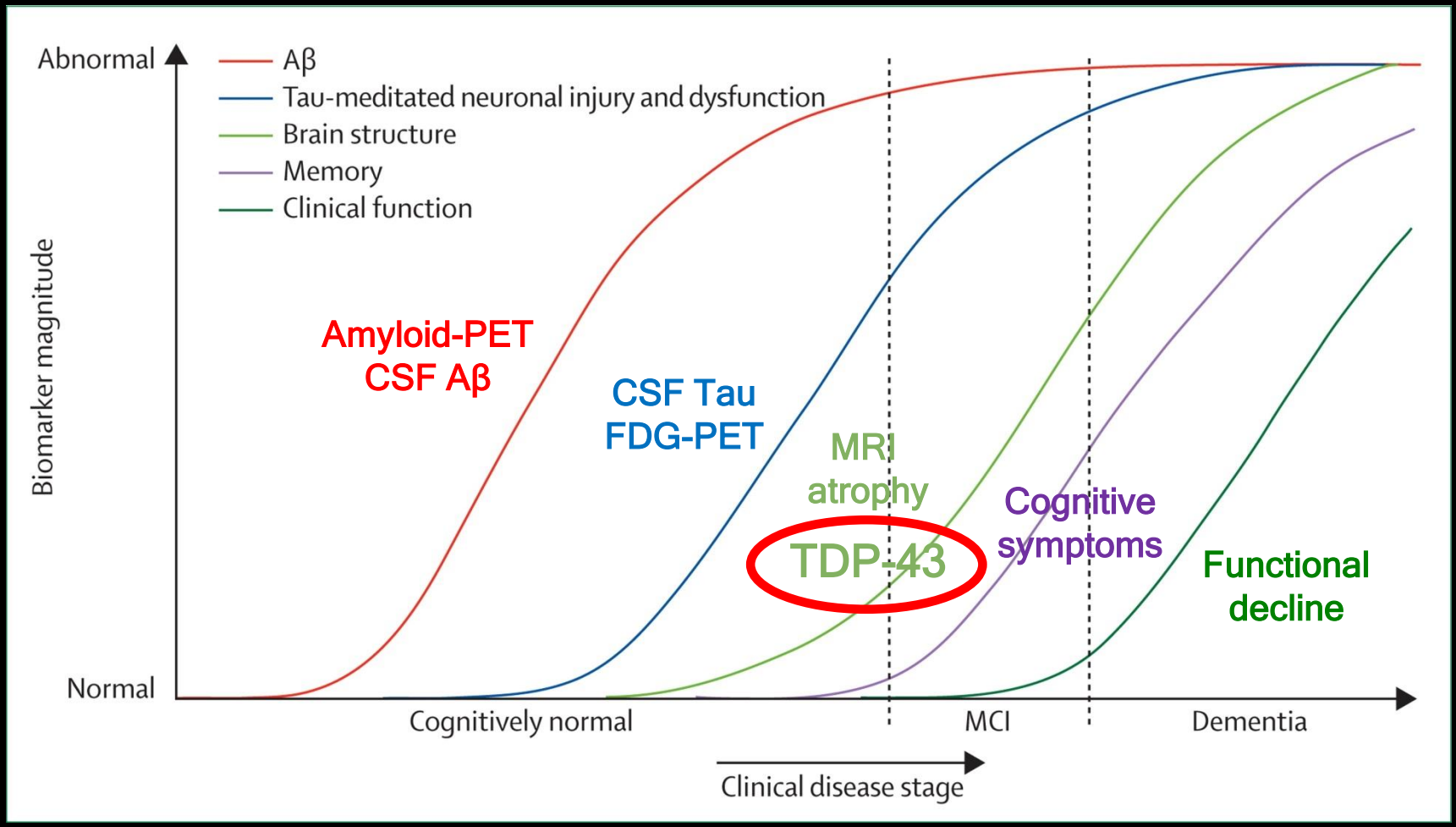

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TDP-43

- Transactive Response DNA-binding Protein 43
- TDP-43 is the most common pathology seen in ALS
- TPD-43 seen in >50% patients AD neuropathology
- Association TDP-43 & cognition independent of plaque, hippocampal sclerosis (Nelson 2008)
- Both tau and TDP-43 major proteins in chronic traumatic encephalopathy (CTE)

So Why FTD?

- Clinically, Alzheimer's is actually messy and a complicated multiproteinopathy
  - Any cure will likely require a cocktail approach

- Frontotemporal Lobar Degeneration (FTLD) syndromes offer cleaner/simpler systems
  - sole tauopathies
  - sole TDP-43opathies

Frontotemporal Dementia

- Selective degeneration of frontal and temporal lobes producing a behavioral dysexecutive syndrome and two language syndromes

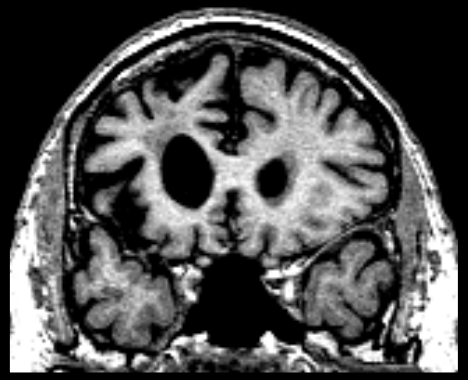
- Common cause pre-senile dementia
  - 1:1 with AD 45–64 years (Ratnavalli, Hodges 2002)
  - More common than AD below 60 yrs (Knopman 2004)
  - 3% clinical prevalence of FTD 80–90 (2003 Skoog)

- Highly genetic

Frontotemporal Dementia (FTD)

Behavioral variant bvFTD

~45% are FTLD-tau
~45% are FTLD-TDP
~10% are AD

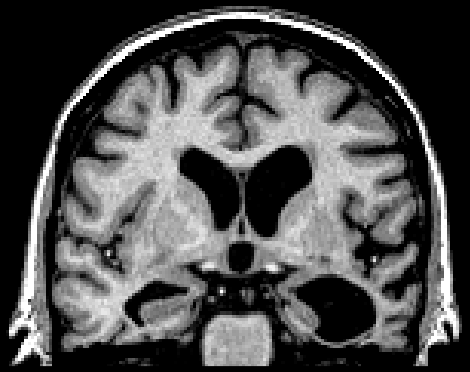


R L

Language variants

Semantic variant svPPA

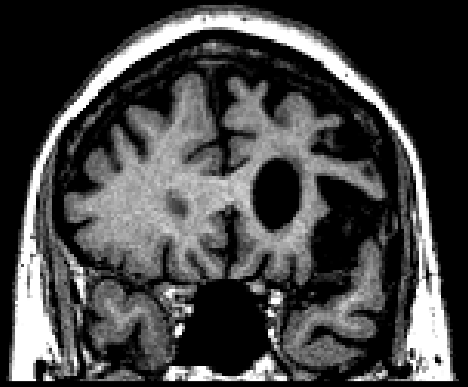
Often FTLD-TDP Type C



R L

Nonfluent variant nfvPPA

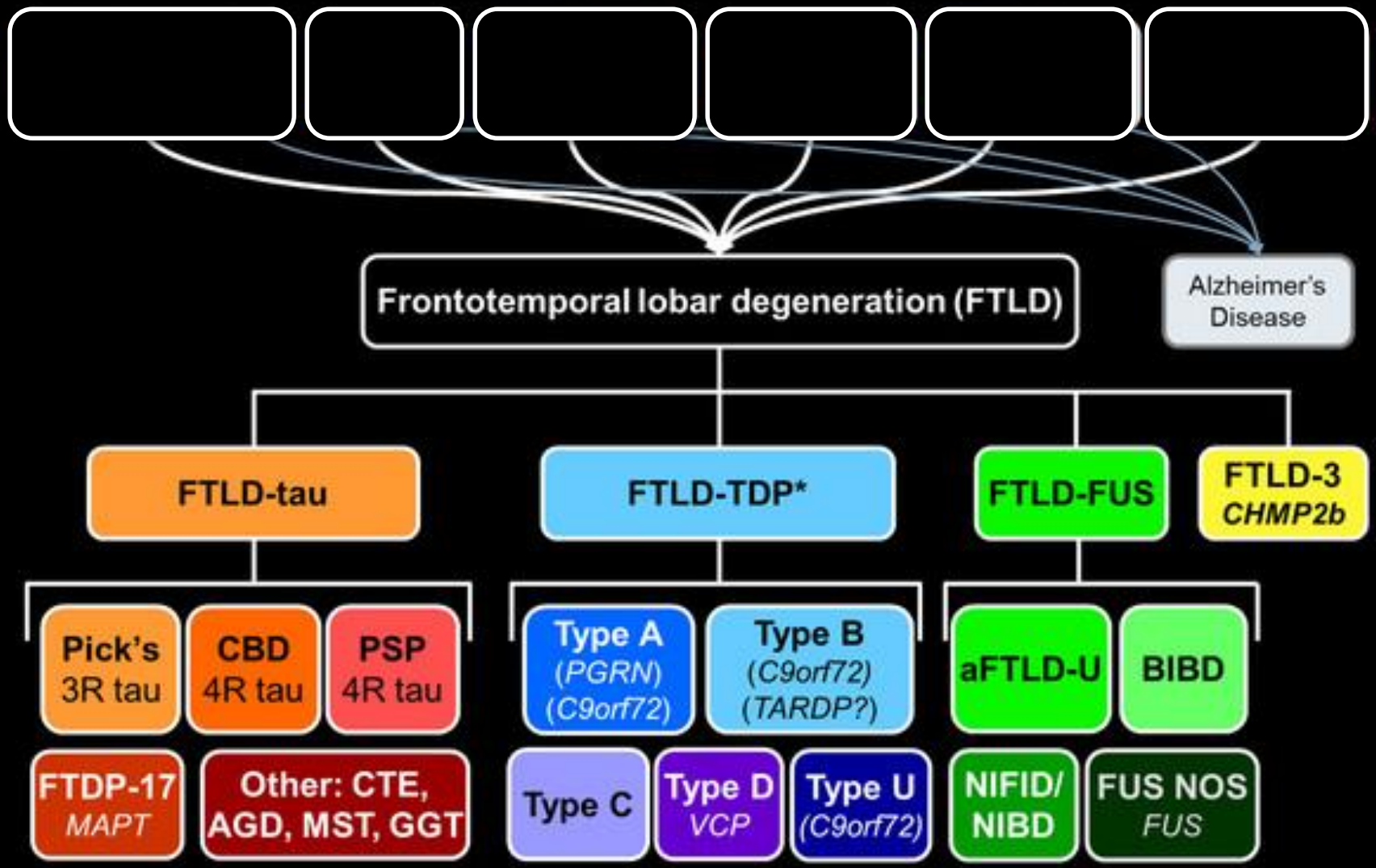
Many tau but can be TDP



R L

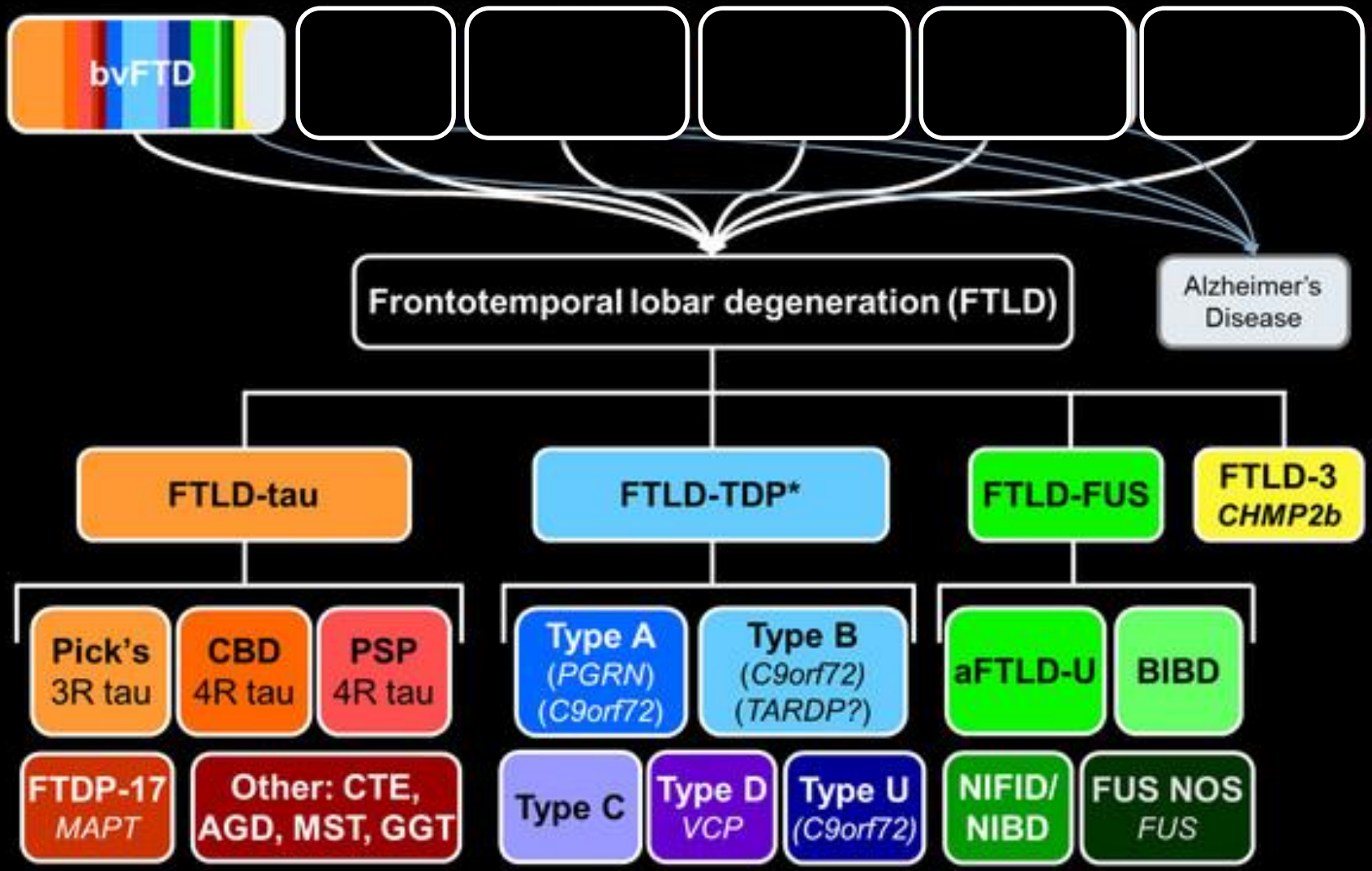
International Research Criteria

- Early (2-3 yrs) behavioral disinhibition
- Early (2-3 yrs) apathy or inertia
- Early (2-3 yrs) loss of emotional reactivity/ sympathy and empathy
- Perseverative, stereotyped or compulsive/ ritualistic behavior
- Hyperorality and dietary changes
- FTD neuropsychological profile
- Frontal and/or anterior temporal atrophy on MRI
- Presence of known mutation



Slide courtesy W. Seeley, UCSF

*Mackenzie harmonized scheme, 2011



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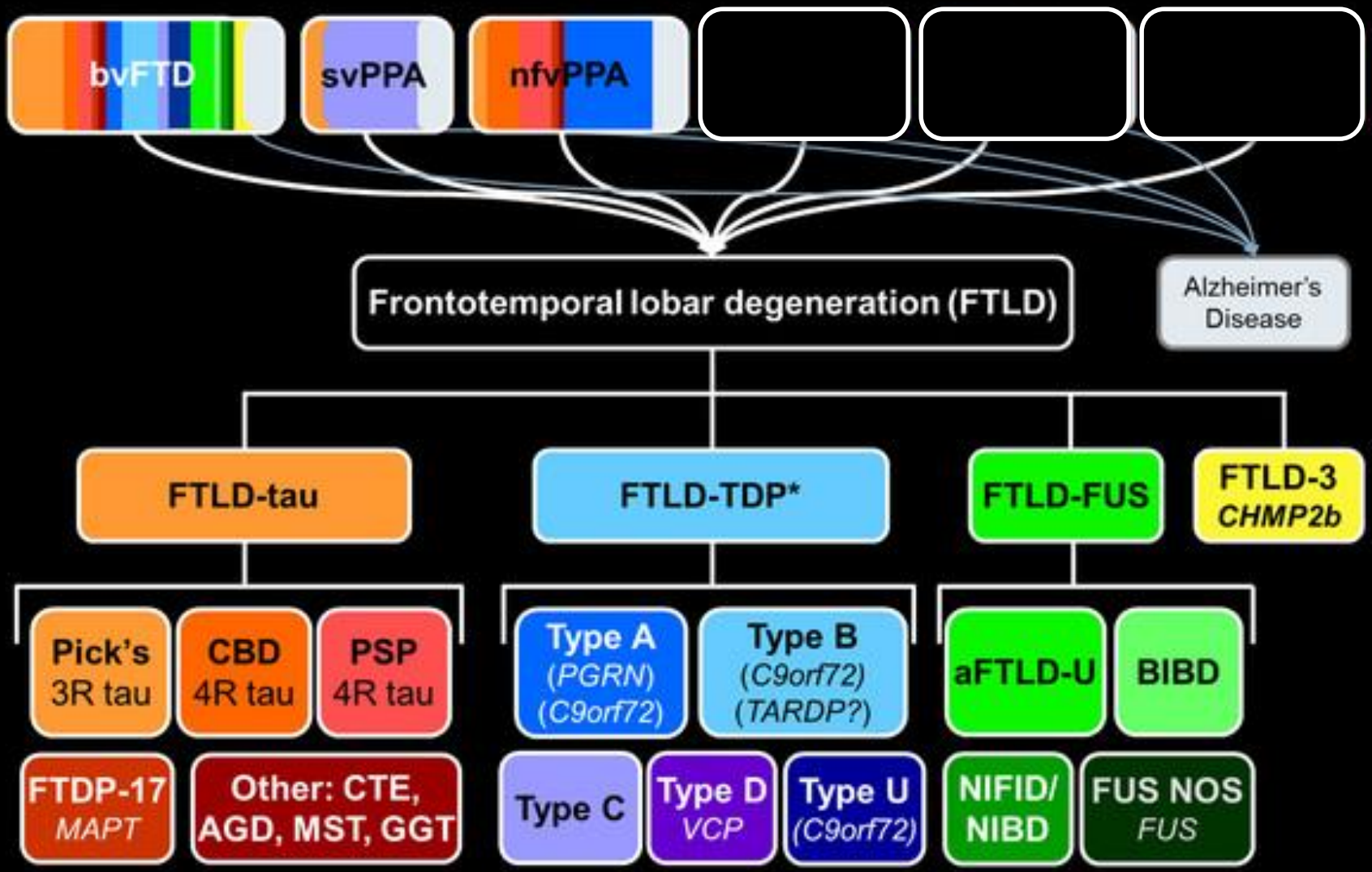

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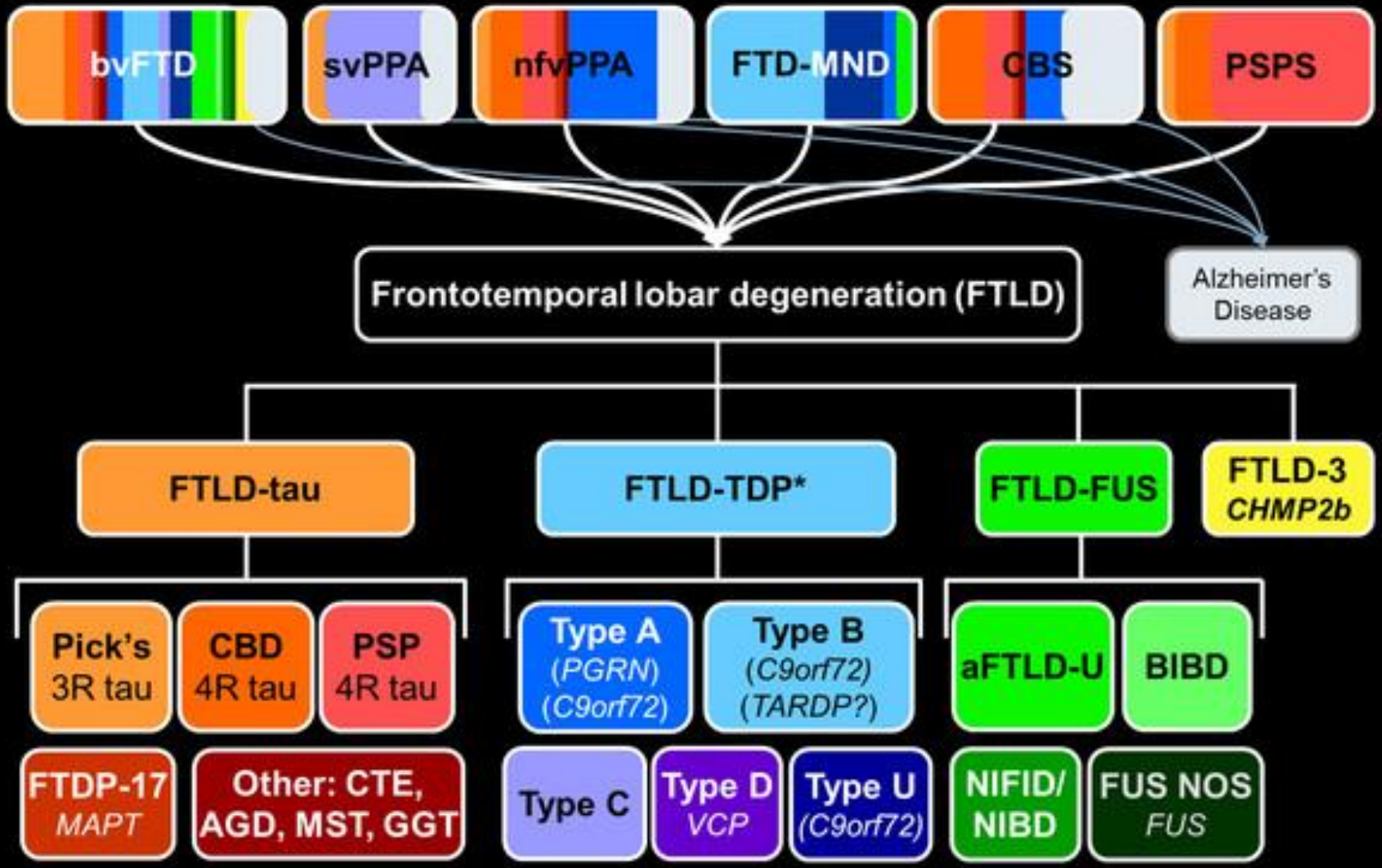

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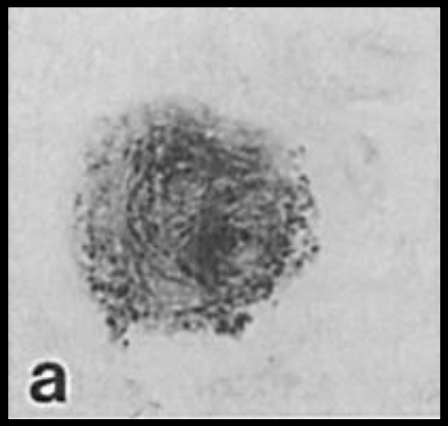
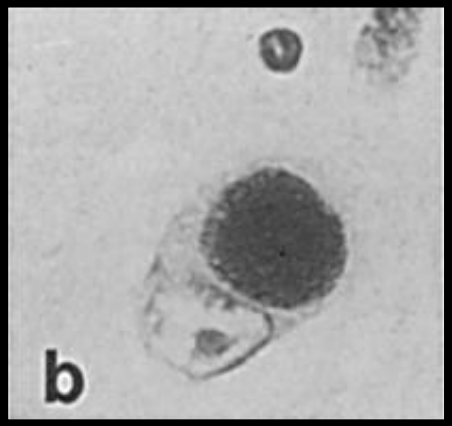
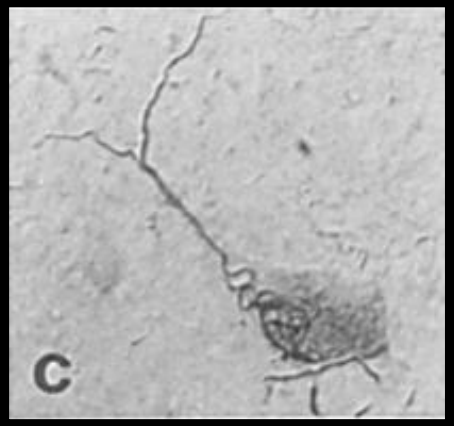
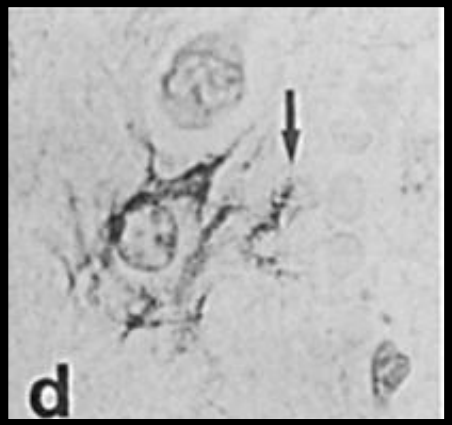
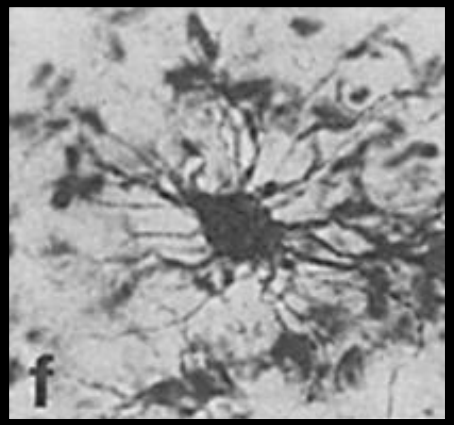
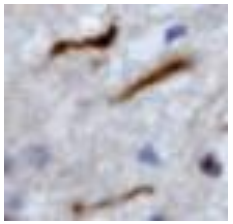
Tau-Immunopositive Inclusions

	PSP 4R tau	Pick's 3R tau	CBD 4R tau
neurons	Globose tangle	Pick body	Coiled tangle
			
astrocytes	Tufted	Dystrophic	Plaque
			

Harmonized Classification for TDP-43 Pathology

TDP-43	Clinical Pathological Correlation	Cortical Path	Dystrophic Neurites 	Neuronal Cytoplasmic Inclusions 	Neuronal Intranuclear Inclusions 
Type A (formerly Type 3 Sampathu and Type 1 Mackenzie)	PGRN, PNFA, bvFTD	Predominantly layer 2	+ + + Short Dystrophic Neurites	+ + +	+ + *Inconsistent feature Frequently present but not neccesary*
Type B (formerly Type 2 Sampathu and Type 3 Mackenzie)	FTLD-MND, bvFTD	All layers	+	+ +	
Type C (formerly Type 1 Sampathu and Type 2 Mackenzie)	PPA-SV, bvFTD	Predominantly layer 2	+ + + *Long* Dystrophic Neurites	+	
Type D (formerly Type 4 Sampathu and Type 4 Mackenzie)	VCP	All layers	+ + + Short Dystrophic Neurites	+	+ + +

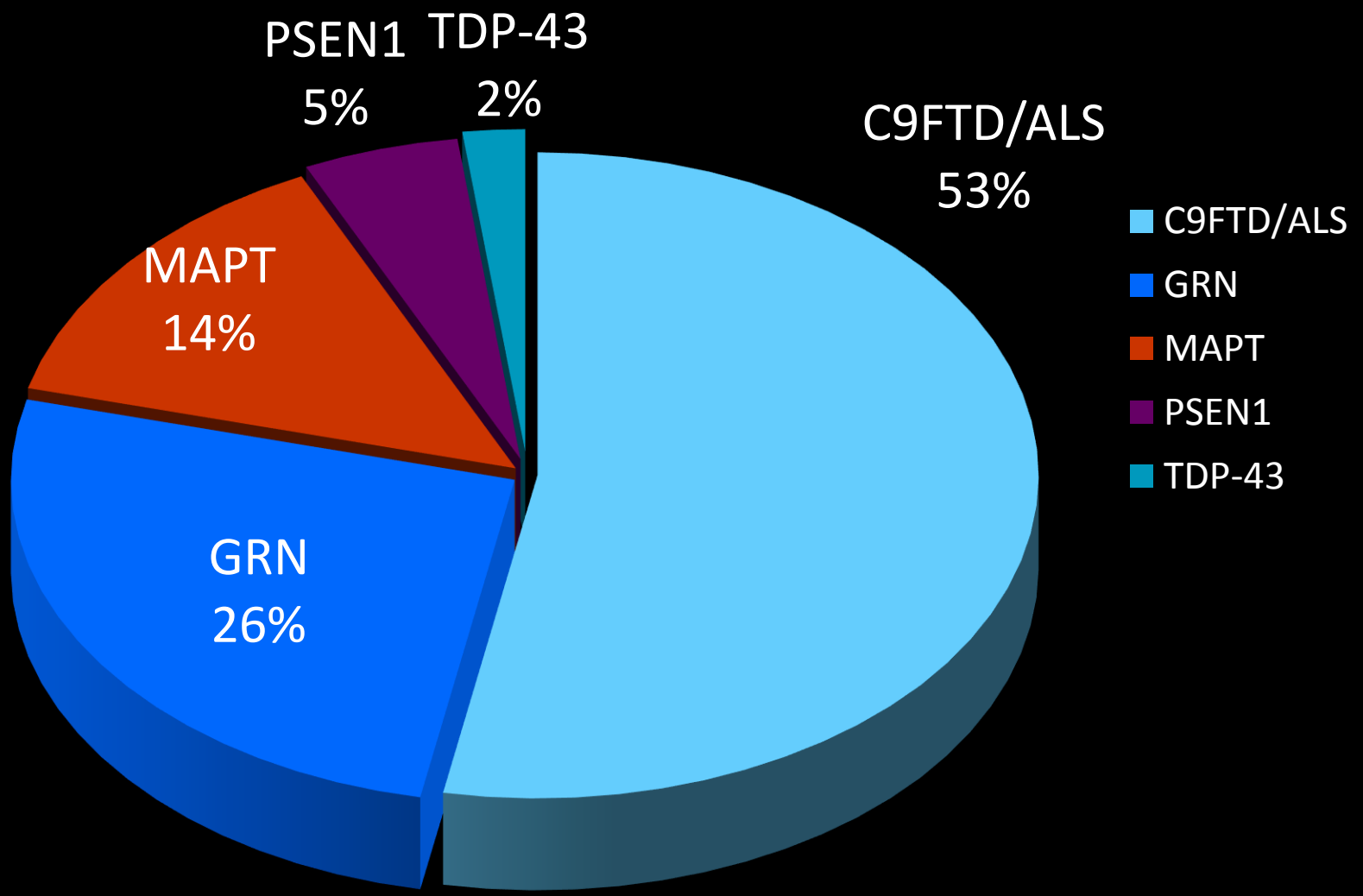
Images adapted from *Manuela Neumann*, *et al.* Science 2006

Schema from *Ian Mackenzie, et al.* Acta Neuropathol 2011

The Big Three

Mutation	C9*orf72*	GRN	MAPT
Ave age of Dx	56	62	52
Clinical presentation	bvFTD, ALS, FTD-ALS	bvFTD, PPA, AD, CBS	bvFTD, PSP, CBS
MRI features	Mild, dorsal, occipital, cerebellar	Asymmetric frontotemporal	Classical frontotemporal
Unique clinical features	ALS, odd psychiatric presentation	Overlap with AD	Suicide and addiction
Biology	TDP-43, RNA-mediated	TDP-43, links to AD, haploinsuffciency	4R tauopathy

Gene Positive Cases at UCSF Memory and Aging Center



North American Network for Genetic forms of FTD

- Recent NIH funded 2 initiatives to study Genetic forms of FTD and conditions with high clinicopathological correlation to FTLD
  - Pts with family histories
    - Known gene status (big 3: C9, GRN, MAPT)
    - Unknown gene status
  - Clinical presentations of FTD-MND
    - Near 100% TDP-43
  - Clinical presentations of PSP
    - Almost always 4R tau

Tauopathies

- Trauma, mutations, polymorphisms, & aging all predispose

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- Pure Tauopathies

- Pick's disease

- Corticobasal degeneration (CBD)

-Progressive supranuclear palsy (PSP)

- Argyrophilic grain disease (AGD)

- Globular glial tauopathies (GGT)

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- Secondary Tauopathies

- Alzheimer's disease

- Aluminum Toxicity

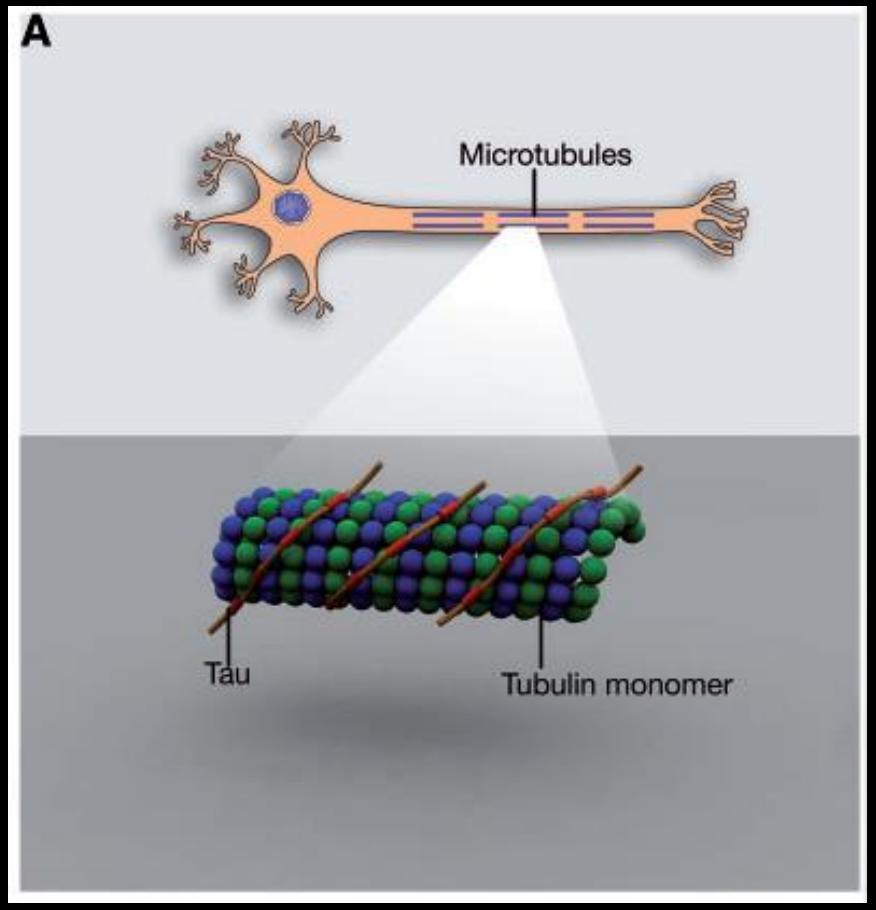
- Niemann-Pick-C

- Guam-ALS-PD-Dementia

- Chronic Traumatic Encephalopathy

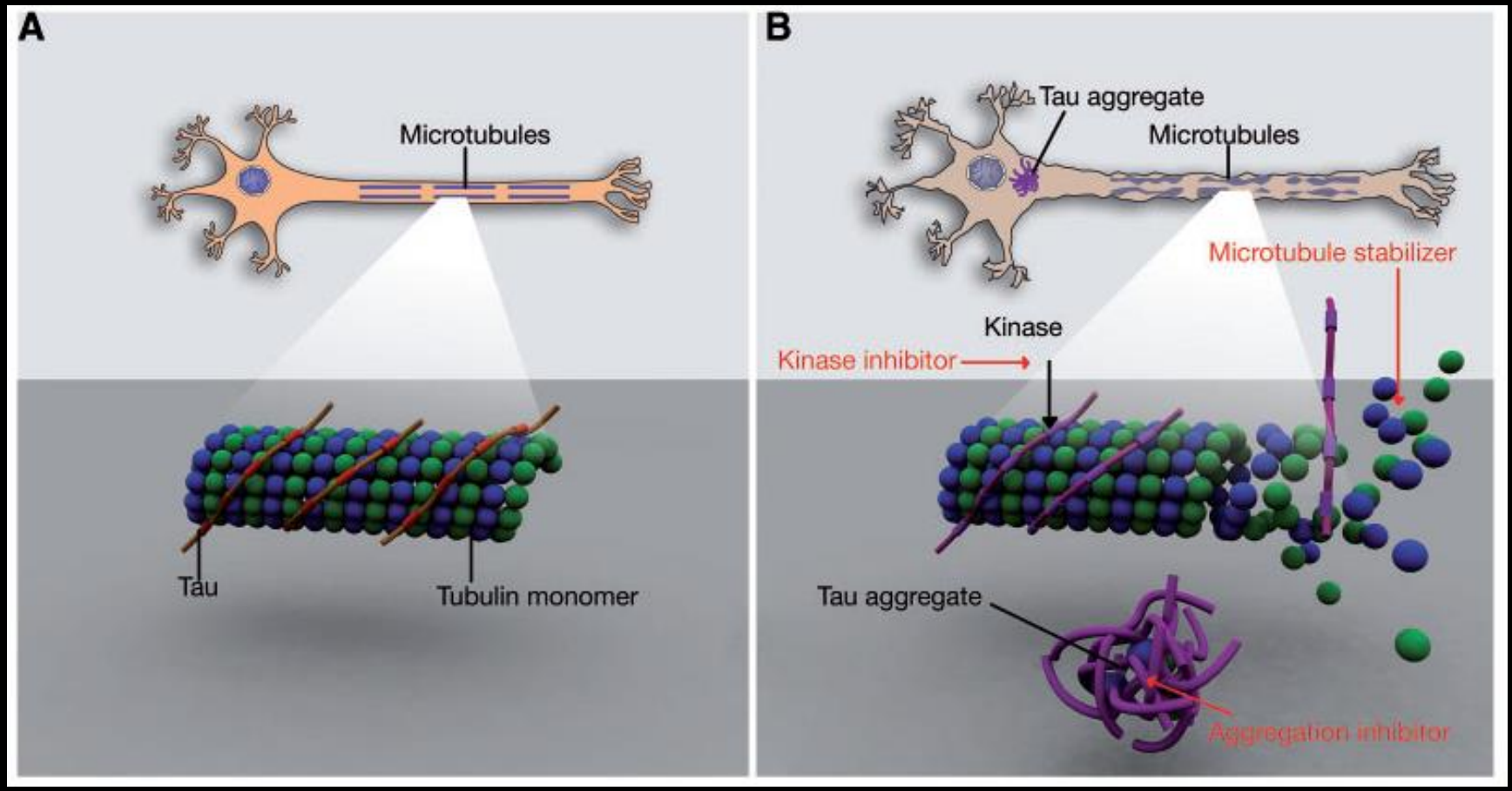
- Post-encephalitic PD

Tau Drug Targets



Stamelou, et al. Brain 2010: 133; 1578-1590

Tau Drug Targets



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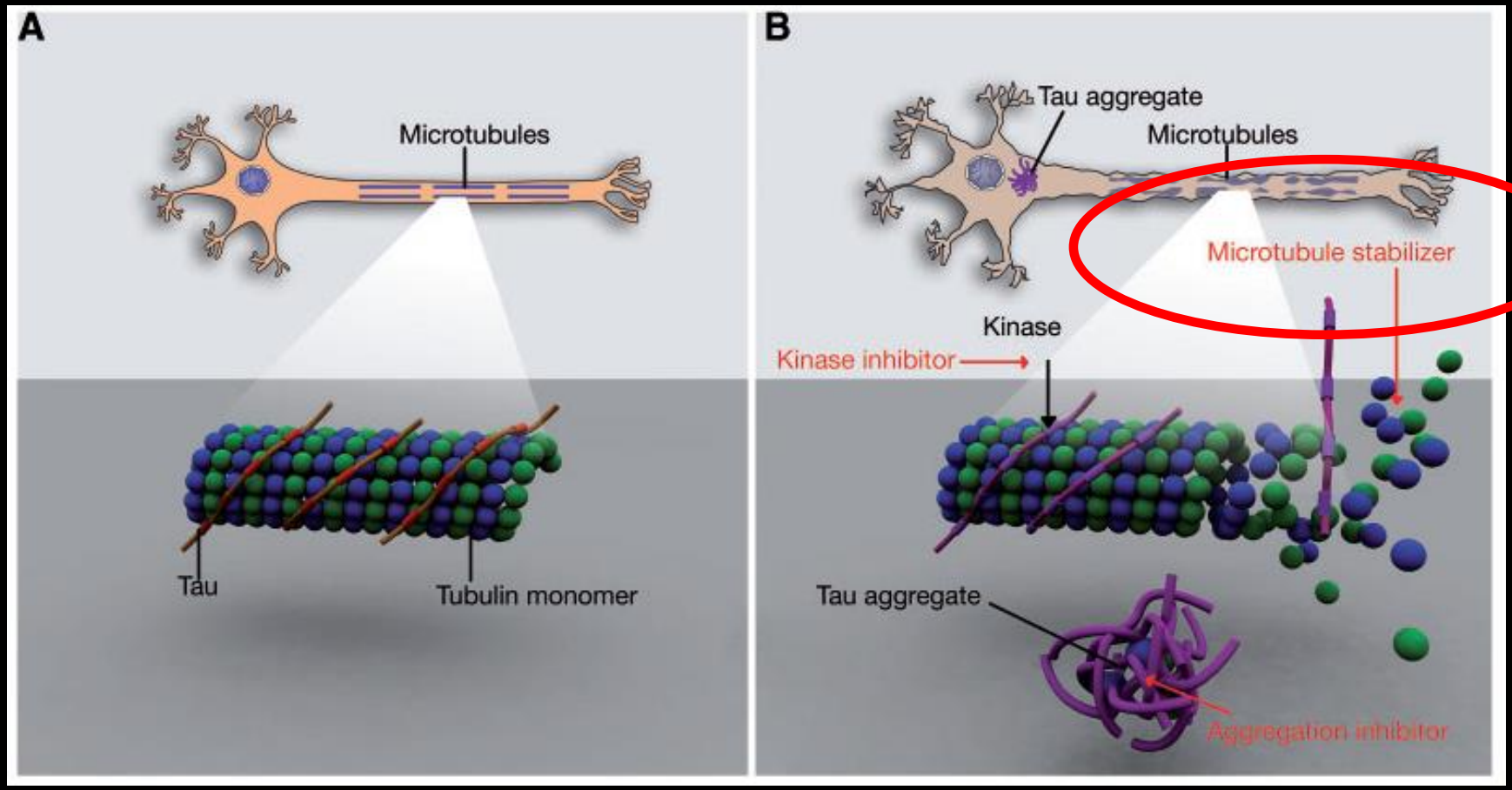

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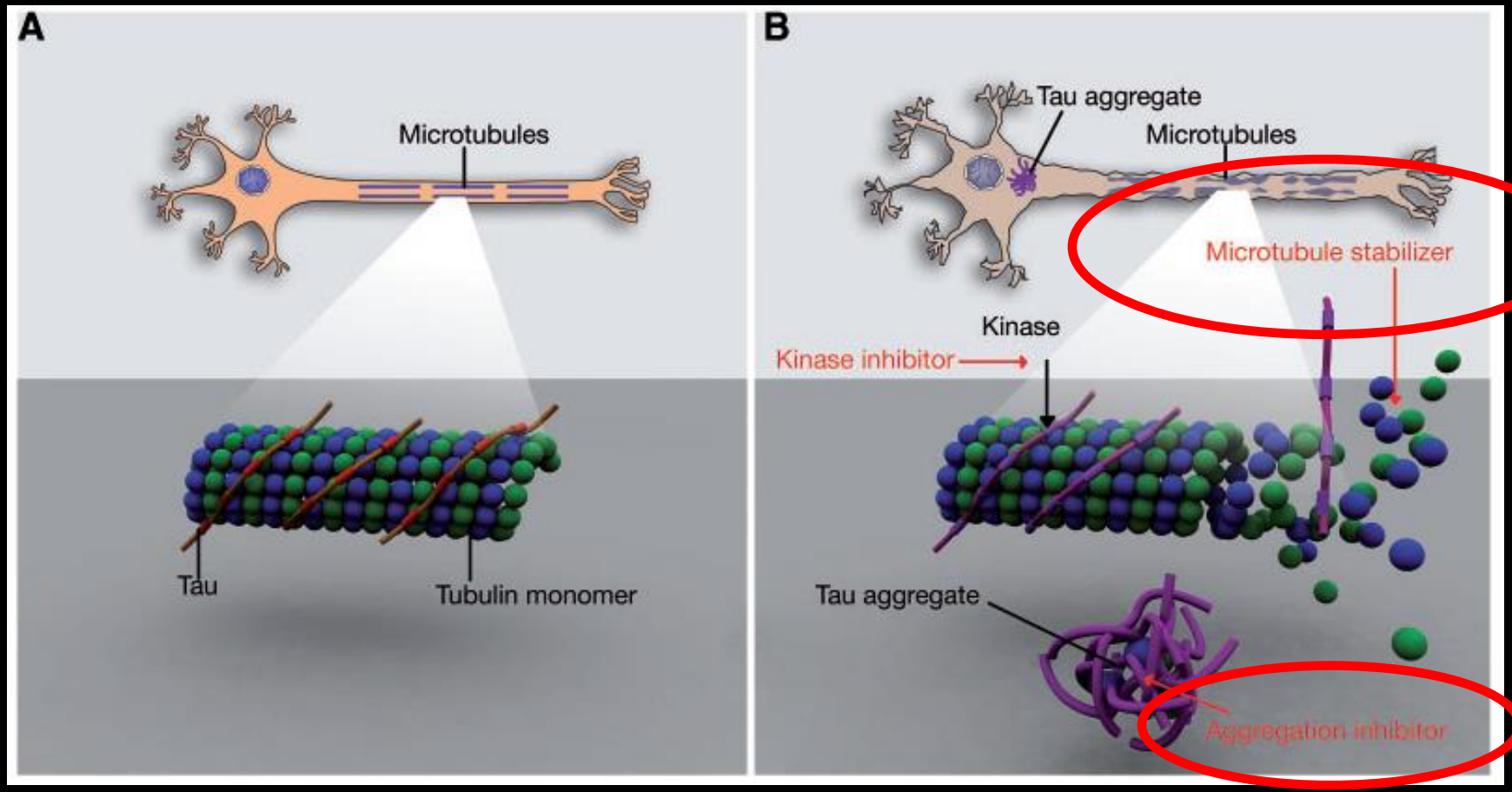


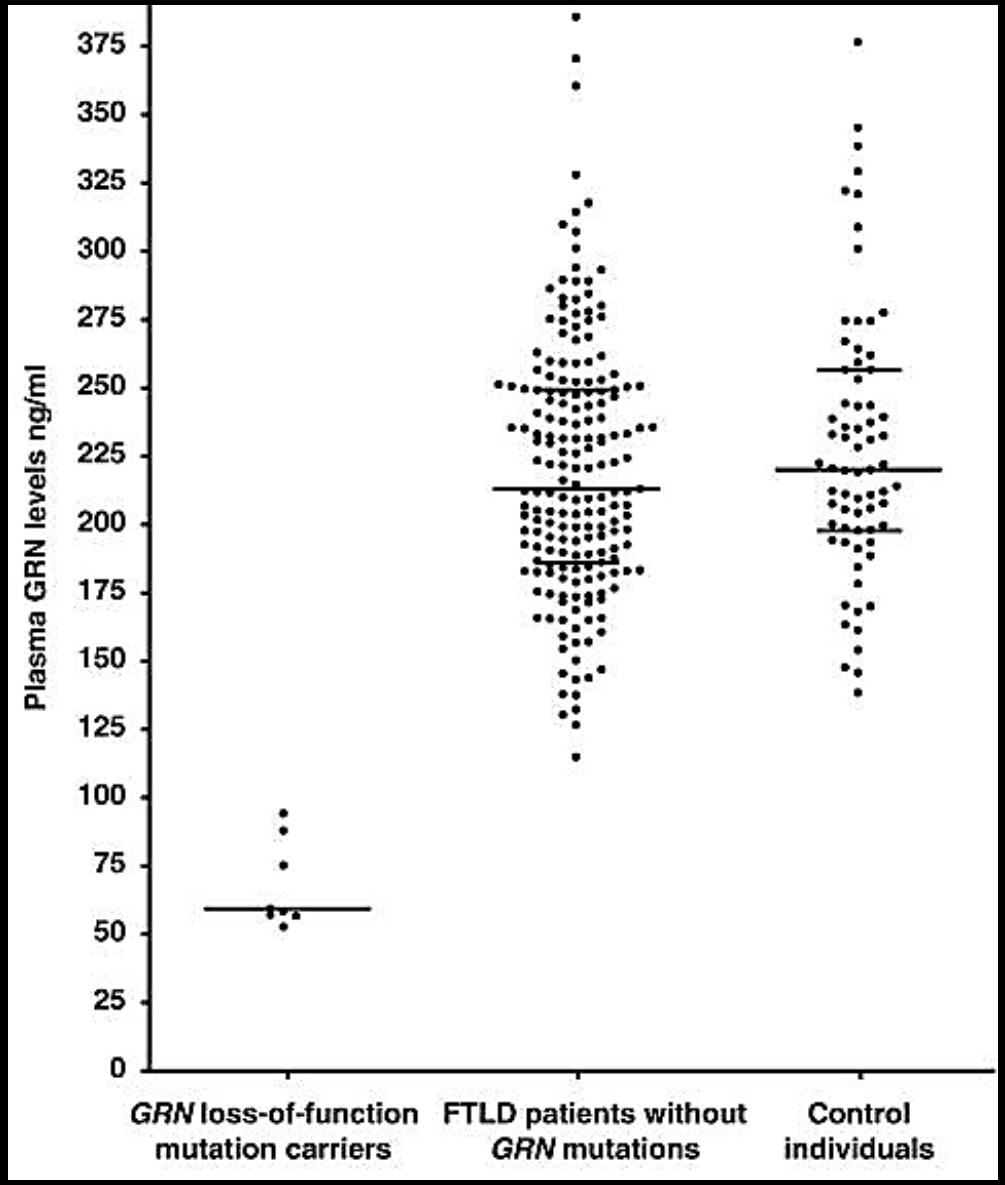
Stamelou, et al. Brain 2010: 133; 1578-1590

PGRN and FTD

- Approximately 20% of inherited FTD results from an autosomal dominant mutation in the progranulin (*GRN*) gene

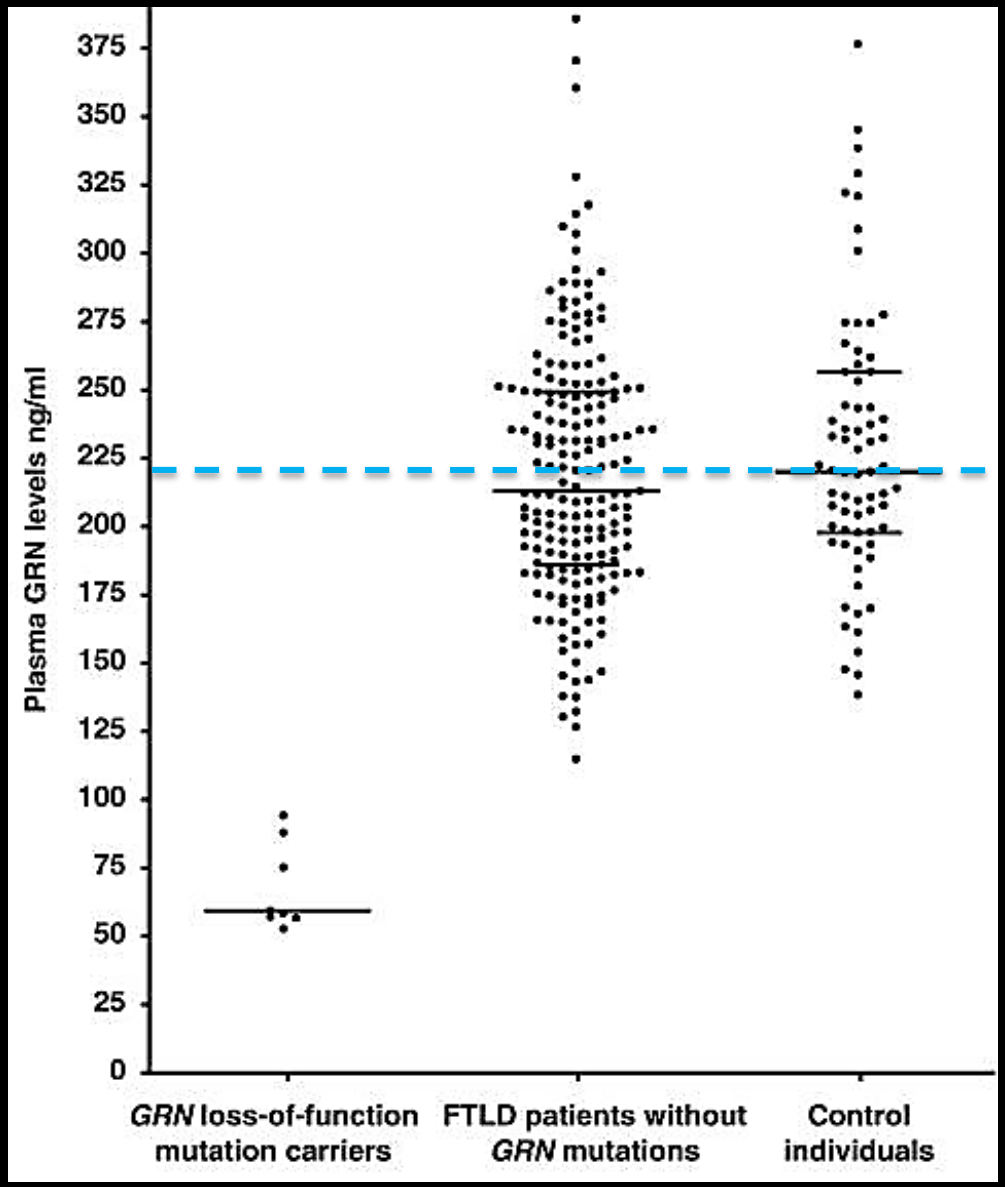
- Produces a haploinsufficiency state with disease associated with serum PGRN levels of less than 50% of normal and results in underlying TDP-43 pathology

PGRN and FTD



Finch et al., 2009

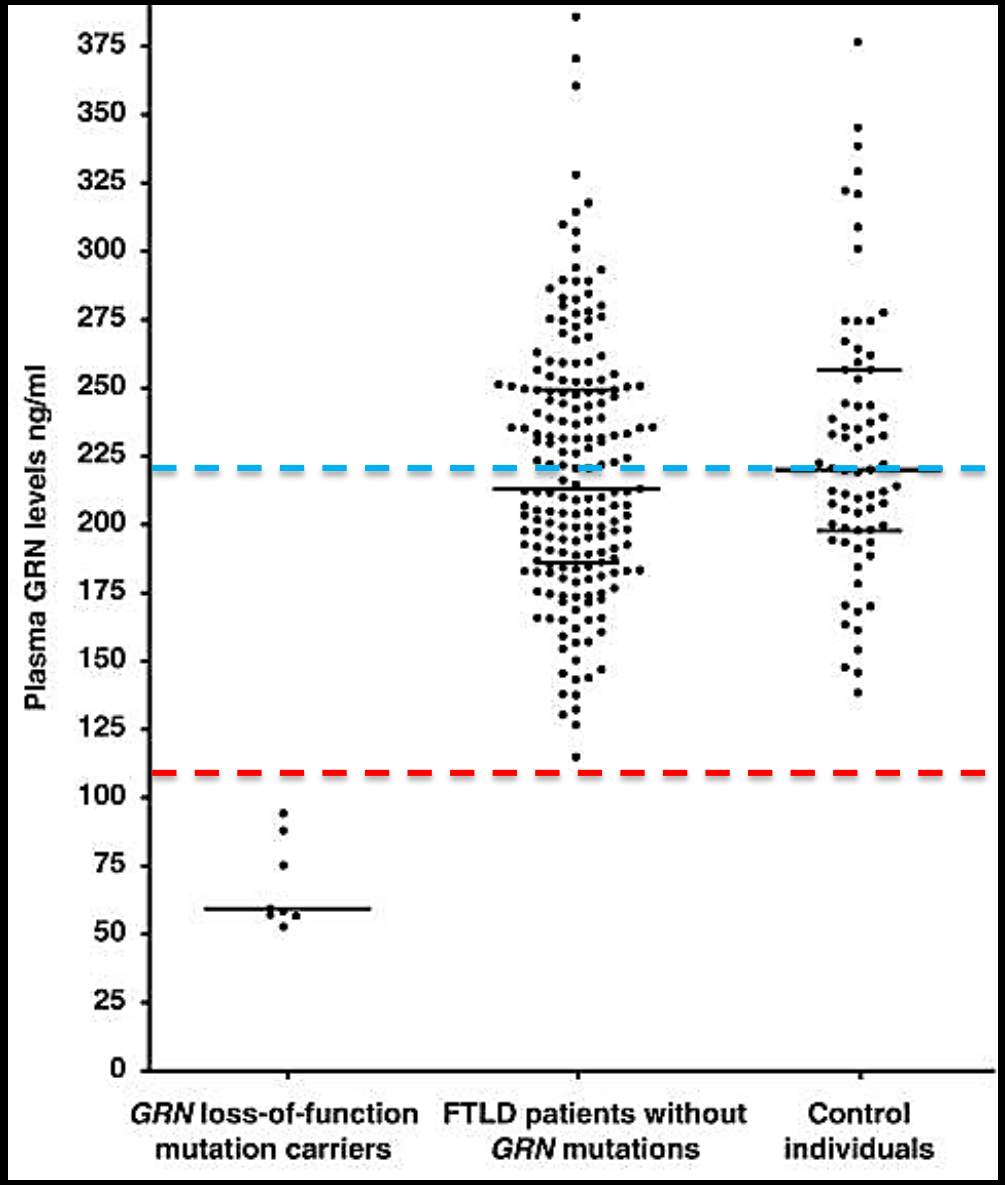
PGRN and FTD



Mean NC

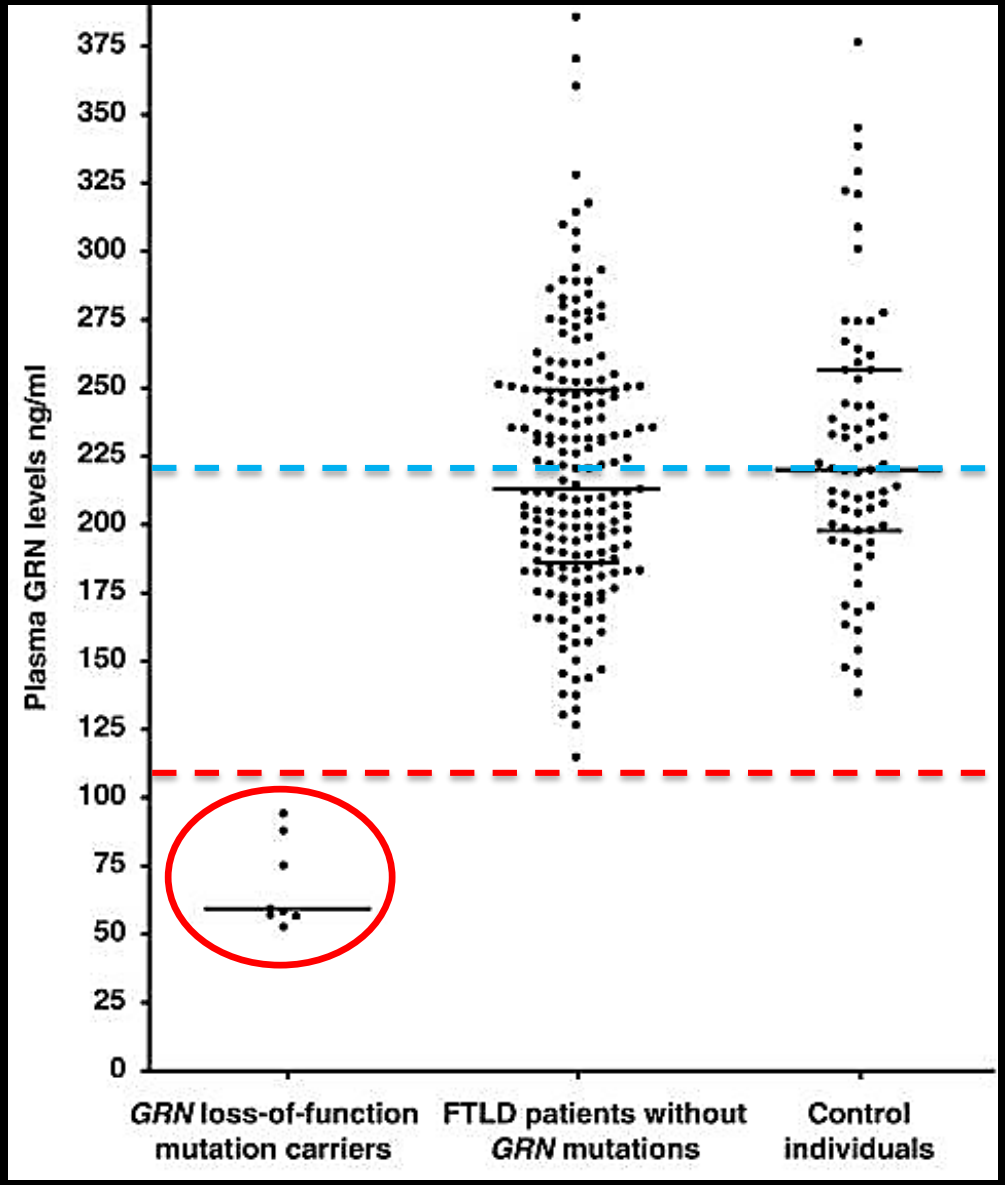
Finch et al., 2009

No NC or GRN- cases below ½ Mean



Finch et al., 2009

And all GRN+ cases below ½ Mean



Finch et al., 2009

PGRN trials

- Current trials geared towards increasing serum PGRN
  - Nimodipine
  - HDAC inhibitors
- Potential future trials looking at modulating immune response
  - My own research focus

Inflammation and Neurodegenerative Disease

- Inflammatory changes evidenced in original pathological descriptions of Alzheimer's
- Lower prevalence AD and PD, respectively, in persons on anti-inflammatory medications
- Genetic mutations associated with AD risk play immunological roles (TREM2, CD33, ABCA1, ABCA7…)

FTD and Inflammation

- Sjögren et al., 2004 noted increased TNF-α in CSF of FTD patients

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- PGRN is known to have wide ranging effects on wound healing and inflammation
- svPPA least genetic FTD syndrome – making it the best target for environmental insult

Table 1 Screen of autoimmune conditions

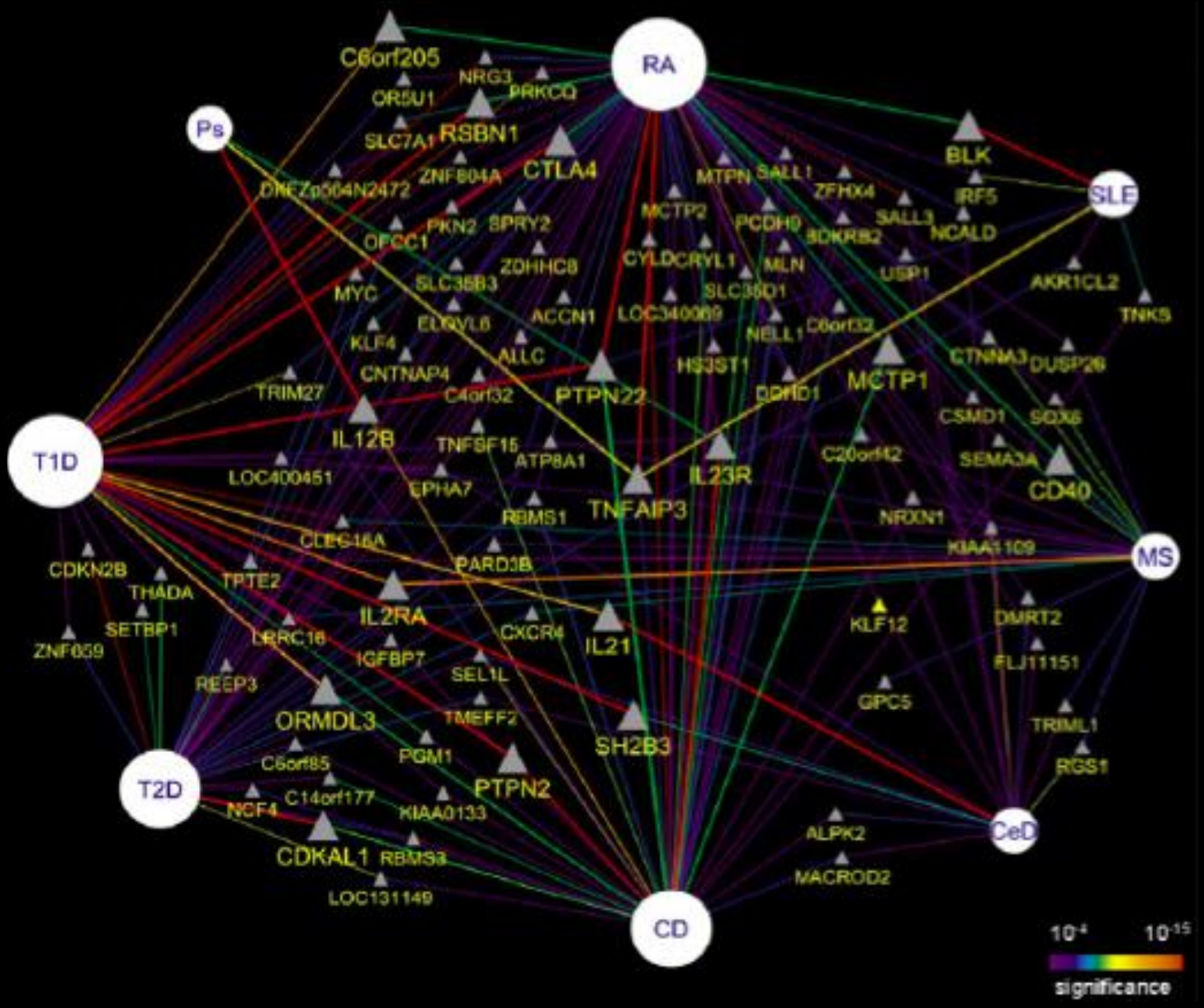
Addison disease	Hashimoto thyroiditis	Psoriasis
Ankylosing spondylitis	Immune thrombocytopenic purpura	Reactive arthritis
Autoimmune haemolytic anaemia	Localised scleroderma	Rheumatoid arthritis
Behcet's disease	Lichen sclerosis	Sarcoidosis
Coeliac disease	Lupoid hepatitis	Sjögren's syndrome
Chorea minor	Multiple sclerosis	Systemic lupus erythematosus
Chronic lymphocytic colitis	Myasthenia gravis	Systemic sclerosis
Chronic rheumatic heart disease	Pernicious anaemia	Type 1 diabetes mellitus
Crohn's disease	Polyarteritis nodosa	Ulcerative colitis
Dermatomyositis	Polymyalgia rheumatic	Vitiligo
Discoid lupus erythematosus	Polymyositis	Wegener granulomatosis
Graves' disease	Primary biliary cirrhosis	

Modified listing of autoimmune conditions screened from Rugbjerg *et al*.[15]

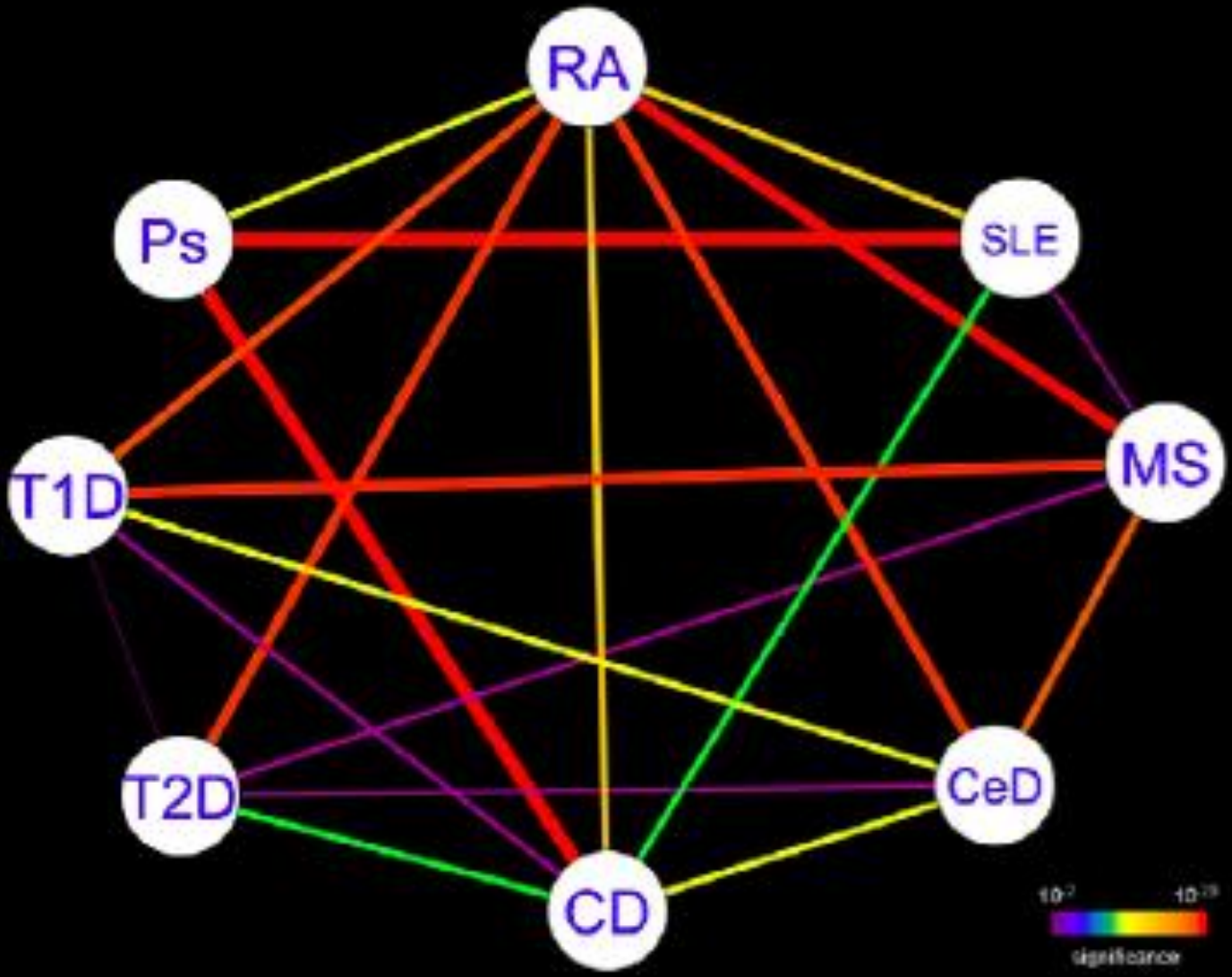
Miller et al., 2013

Brief discussion of autoimmune dz

- Particular conditions cluster in families and co-occur within the same patient
- Some exist on a spectrum of pathological and diagnostic criteria – *Rhupus*
- Modern genetic analysis helped to delineate the interrelationships



Baranzini et al., 2009

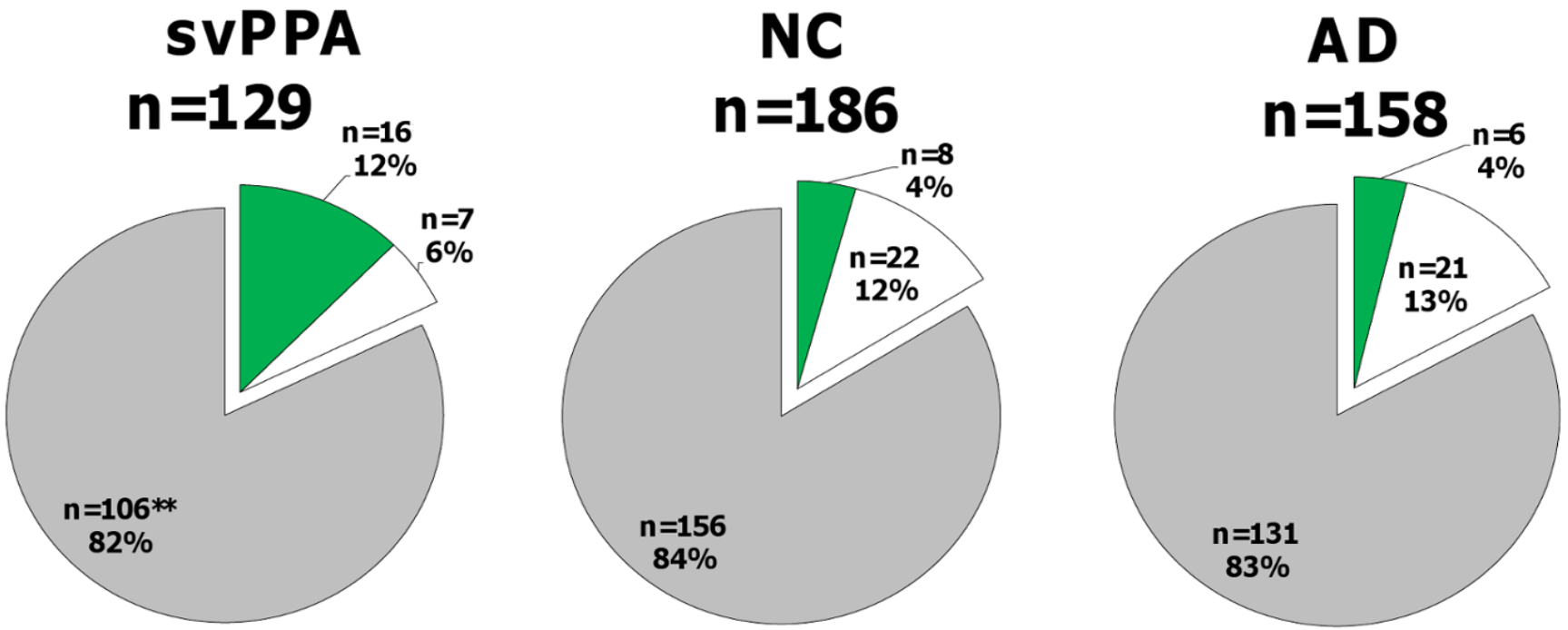


Baranzini et al., 2009

Not All Autoimmune Diseases are the Same

- While increasing evidence shows connections between autoimmune disorders, not all autoimmune diseases are the same

- Some conditions appear to be inversely correlated
  - Sirota et al., 2009 showed that alleles specific to RA had an inverse relationship to autoimmune thyroid disease



16 Others:
Chronic Lymphocitic Colitis & Thyroid (n=1)
Discoid Lupus & Systemic Lupus Erythematosus (n=1)
Lichen Sclerosis (n=1)
Psoriasis (n=1)
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Type 1 Diabetes Mellitus & Thyroid (n=1)*
Vitiligo (n=1)
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8 Others:
Ankylosing Spondylitis (n=1)
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6 Others:
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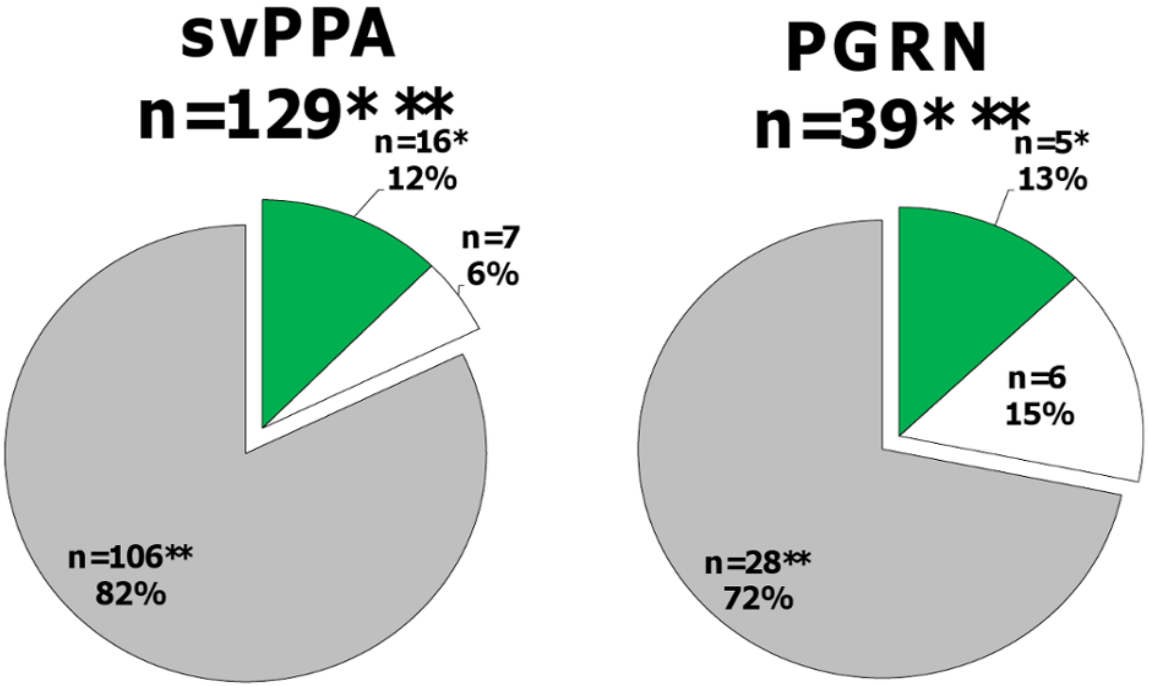
Other Autoimmune | Thyroid Only | Nothing Mentioned

Miller et al., 2013



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Autoimmune clusters in svPPA & PGRN

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   - Rheumatoid Arthritis
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- Chronic Lymphocytic Colitis

Table 4 Comparison of autoimmune prevalence

Autoimmune disease	PGRN+svPPA cohort prevalence	Estimated general population prevalence	Estimated OR
Thyroid (hypo and hyper)	10.2% (n=17*)	8.9%–10.3%[19 20]	0.99–1.15
Psoriasis	1.8% (n=3)	0.1%[21]	18
Rheumatoid arthritis	1.8% (n=3)	0.86%[16 22 23]	2.1
Sjögren's	1.8% (n=3)	0.014%–0.32%[16 24]	5.6–107.14
Sarcoidosis	1.8% (n=3)	0.001%–0.04%[25]	45–1800
Vitiligo	1.8% (n=3)	0.4%[16 26]	4.5
Systemic lupus erythematosus	1.2% (n=2)	0.024%[16]	50
Coeliac disease	0.6% (n=1)	0.83%–0.03%[27]	0.72–20
Chronic lymphocytic colitis	0.6% (n=1)	0.06%[28]	10
Discoid lupus	0.6% (n=1)	0.4%–0.8%[29]	0.75–1.5
Lichen sclerosis	0.6% (n=1)	Unknown[18]	NA
Type 1 diabetes mellitus	0.6% (n=1*)	0.19%[16]	3.16

*Patient with clinical svPPA and PGRN carrier who has type 1 diabetes mellitus and thyroid disease.
PGRN, progranulin; svPPA, semantic variant primary progressive aphasia.

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Validation?!

- Since closing our data set we continue to observe more cases of the same autoimmune conditions within our svPPA cohort
  - Psoriasis, RA, Sjögren's syndrome, Vitiligo…

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- Since closing our data set we continue to observe more cases of the same autoimmune conditions within our svPPA cohort
  - Psoriasis, RA, Sjögren's syndrome, Vitiligo…
- Turner et al., 2013 published *Autoimmune disease preceding amyotrophic lateral sclerosis: An epidemiologic study*

Validation?!

- Since
  - Pso
- Turn

ALS and some forms of FTD are unified by the presence of cytoplasmic inclusions of the transactive response DNA-binding protein 43 (TDP-43). A case-control study of the prevalence of autoimmune diseases across the phenotypic range of TDP-43–associated FTD revealed significant associations among those with semantic variant primary progressive aphasia, and familial cases linked to *PRGN* mutations. Although small numbers of patients were involved, several of the autoimmune diseases we describe in association with ALS were specifically noted, including diabetes, celiac disease, Sjögren syndrome, systemic lupus erythematosus, thyroid disease, and colitis.[26]

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Validation?!

- Since
  - obse
  - cond
    - Psc
- Turn
  - *disec*
  - *scler*

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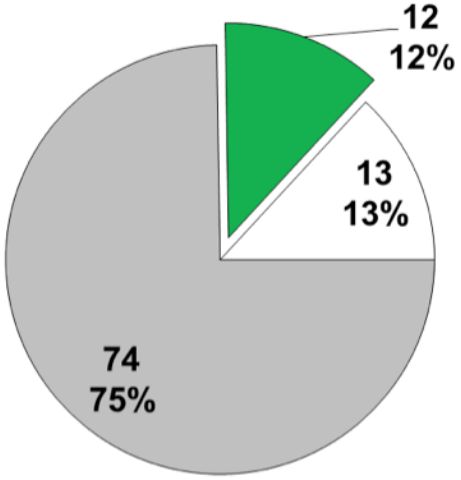
C9 & FTD/MND n=99



NC n=186

8 Others:

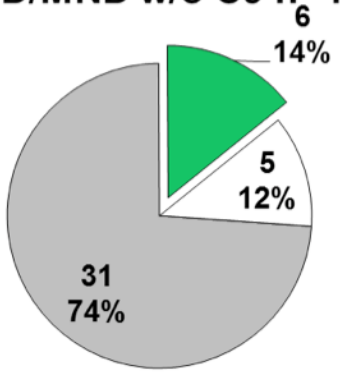
Ankylosing Spondylitis (n=1)
Psoriasis (n=2)
Rheumatoid Arthritis (n=2)
Sacroidosis (n=1)
Ulcerative Colitis (n=2)

AD n=158

6 Others:

Celiac & Type 1 Diabetes Mellitus (n=1)
Rheumatoid Arthritis (n=3)
Rheumatoid Arthritis & Sjögren's Syndrome (n=1)
Ulcerative Colitis (n=1)

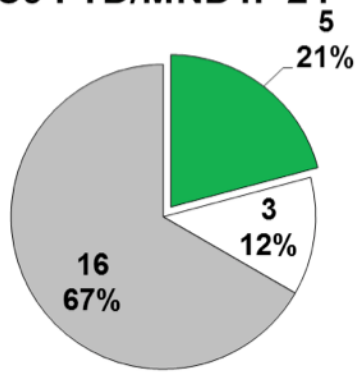
FTD/MND w/o C9 n=42



6 Others:

Ankylosing Spondylitis (n=1)
Crohn's (n=1)
Rheumatoid Arthritis (n=1)
Sarcoidosis & Transverse Myelitis (n=1)
Ulcerative Colitis & Thyroid (n=1)
Vitiligo (n=1)

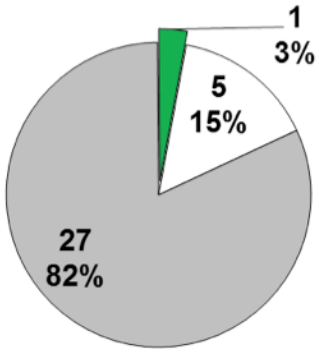
C9 FTD/MND n=24



5 Others:

Ankylosing Spondylitis (n=1)
Celiac (n=1)
Crohn's (n=1)
Lichen Sclerosis (n=1)
Psoriasis (n=1)

C9 FTD only n=33



1 Other:

Vitiligo (n=1)

Non-Thyroid Thyroid only Nothing mentioned

Further Validation?!

- GWAS in FTD revealed 2 significant hits
  - HLA locus
  - RAB38
- HLA is well known to play roles in inflammation and autoimmunity
- RAB38 is involved in melanin pigment transportation
  - involved in pathomechanisms of Vitiligo (the most common autoimmune disease within all FTLD-TDP)

PGRN and Autoimmune Disease

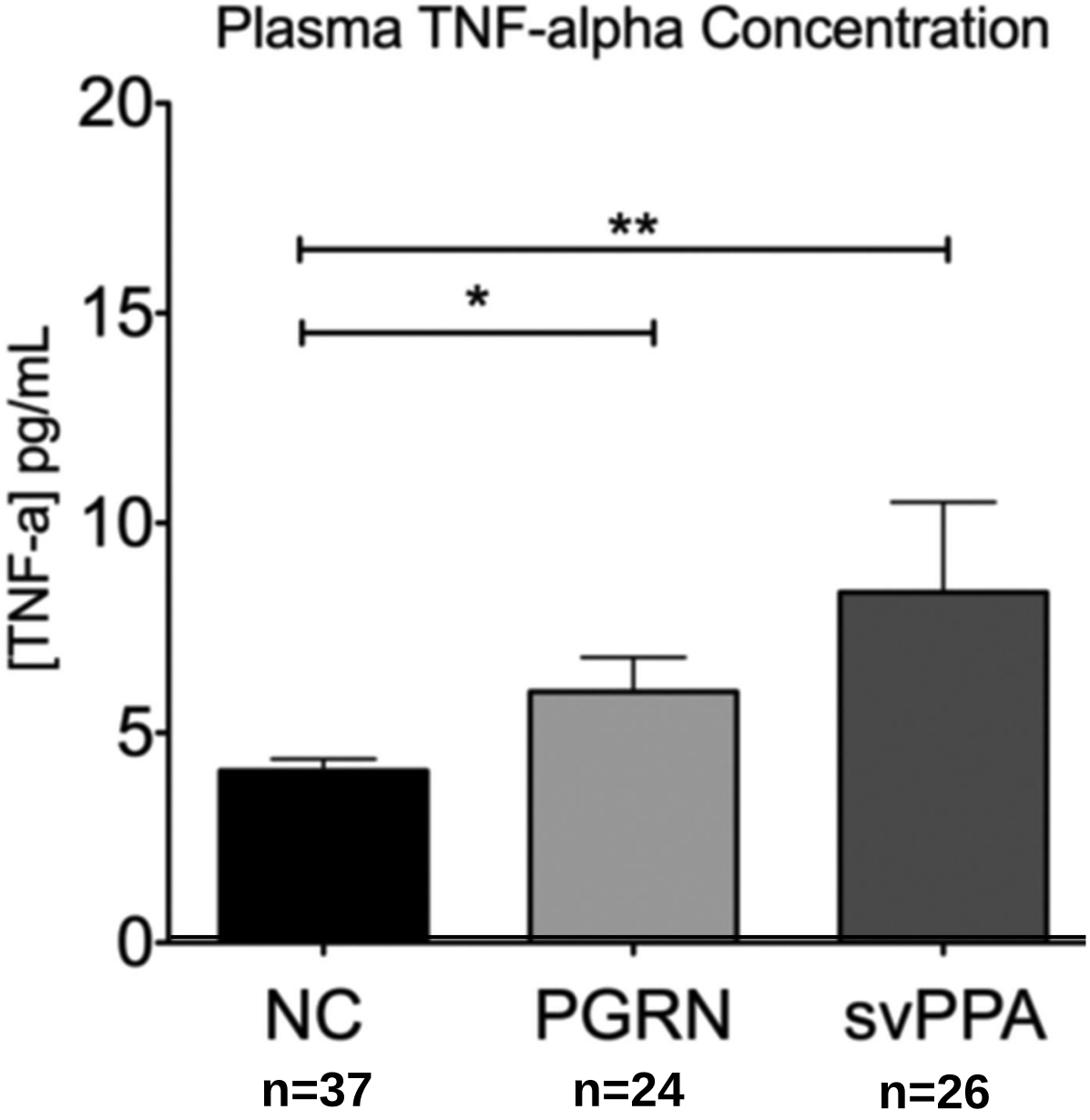
- Tang et al., 2011 PGRN knockout mice revealed
  - increased TNF-α signaling
  - Increased susceptibility to collagen-induced inflammatory arthritis
  - rescued with exogenous PGRN

- Demonstrated that PGRN binds TNFR blocking TNF-α signaling

TNF-α and Autoimmune Disease

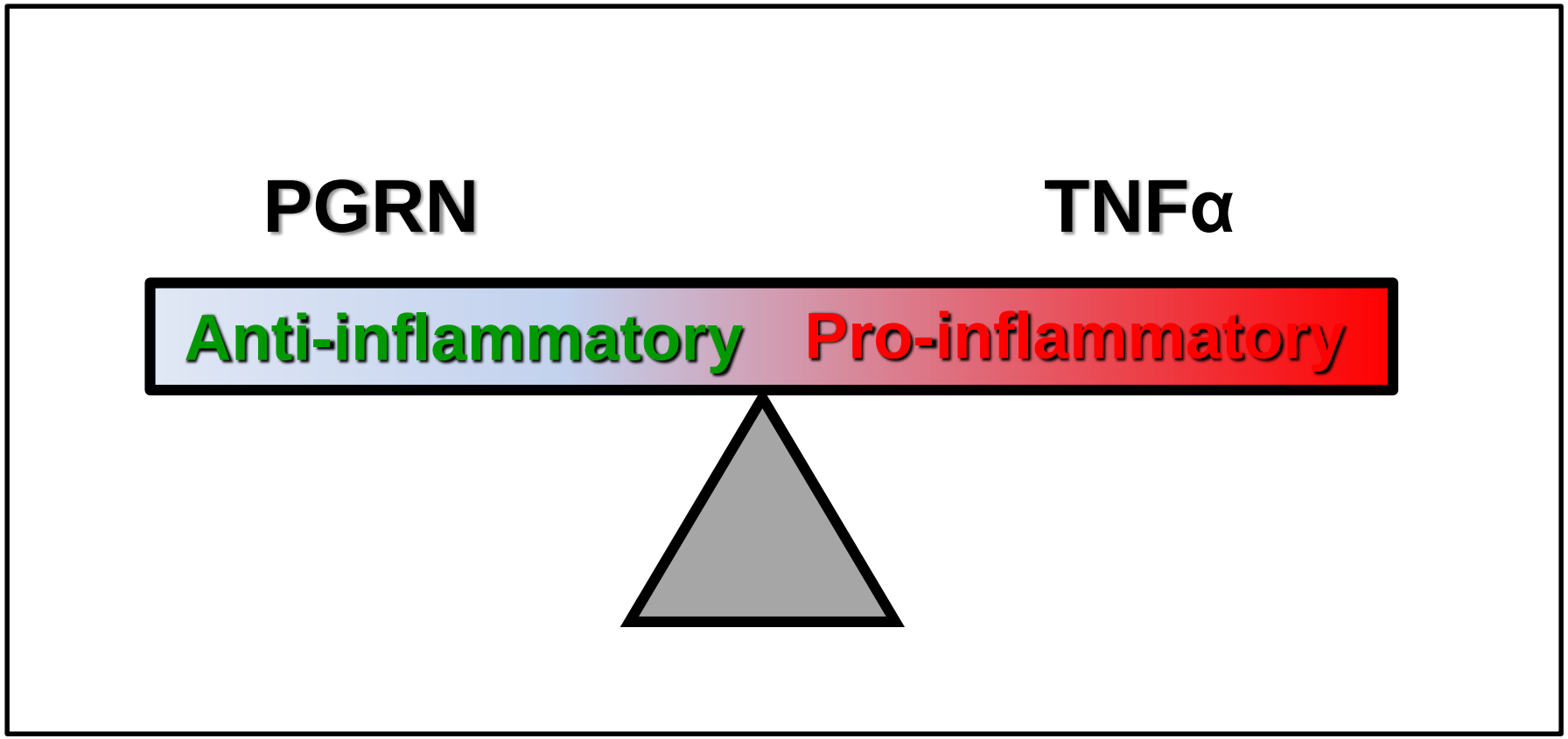
- TNF-α is a potent proinflammatory cytokine
  - member of the TNF superfamily
  - involved in regulation of wide range of immunological activities – proliferation, differentiation, apoptosis…
  - principle cytokine that mediates acute inflammation

- TNF-α signaling plays a central role in the pathogenesis of RA, Sjögrens syndrome, Psoriasis, and many other autoimmune disorders



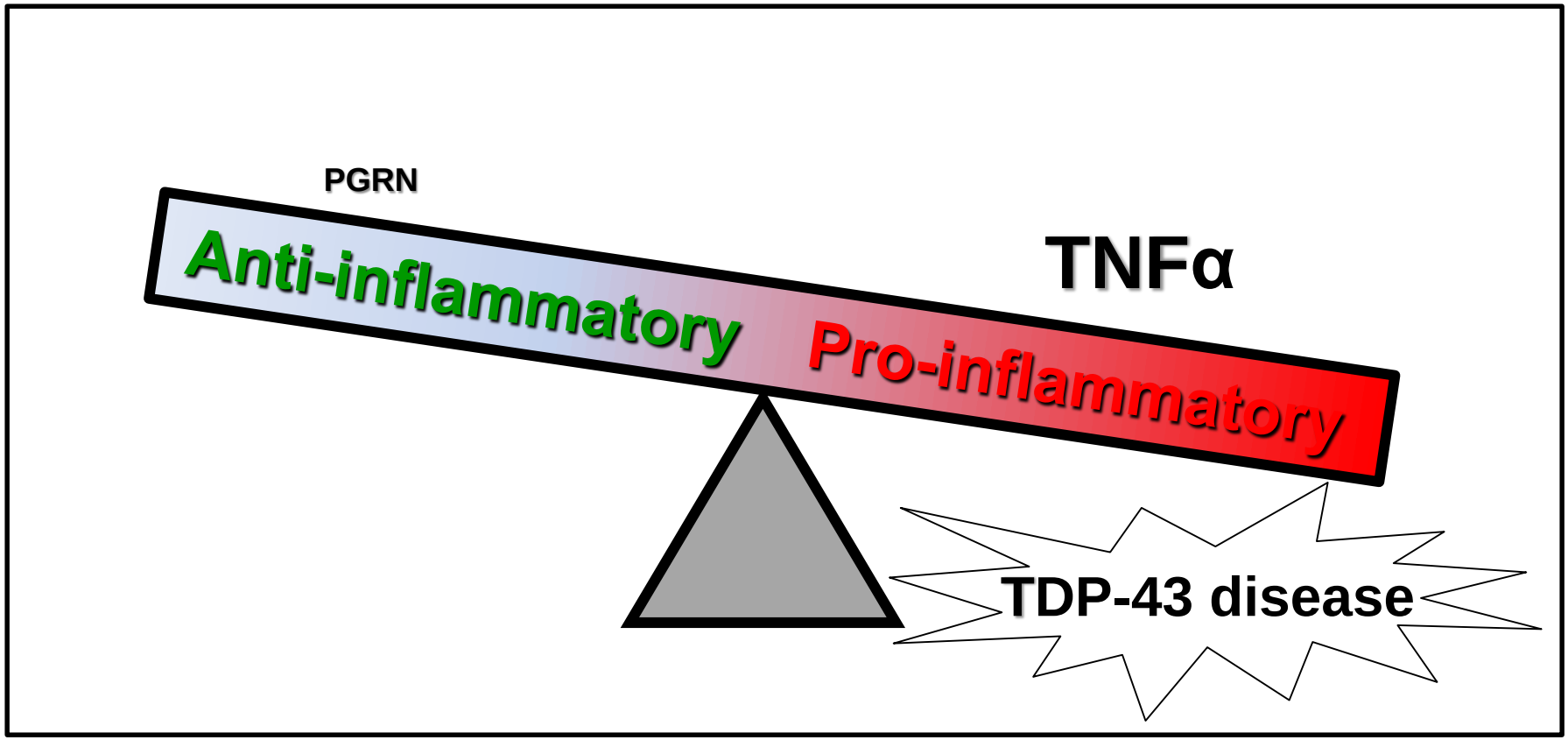
Miller et al., 2013

Normal Inflammation Homeostasis



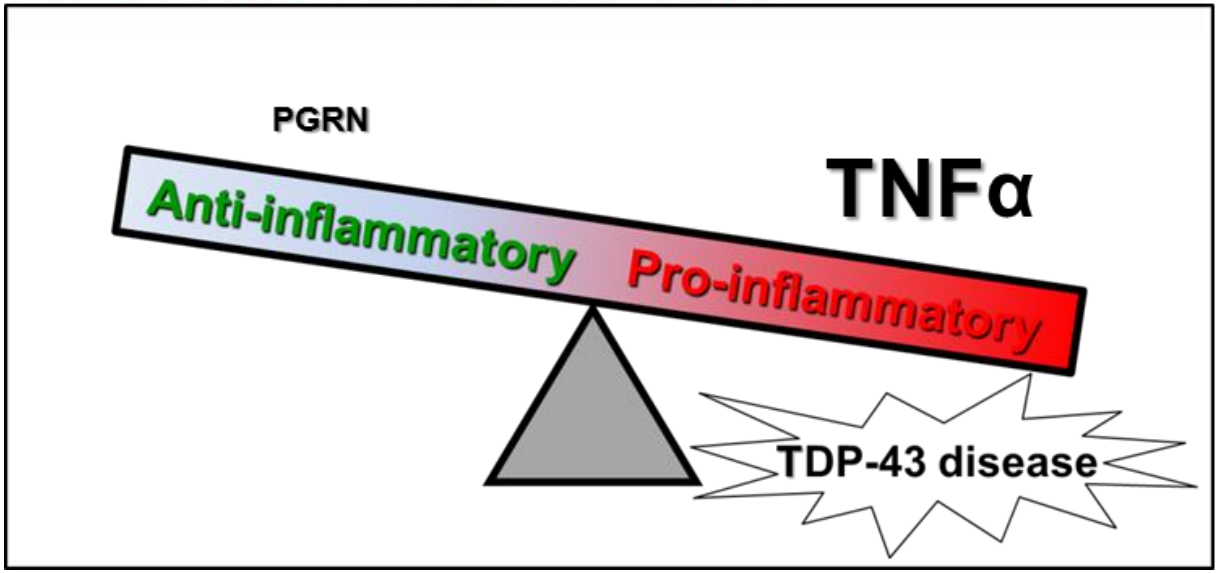
Miller et al., 2013

Disruption due to loss of PGRN

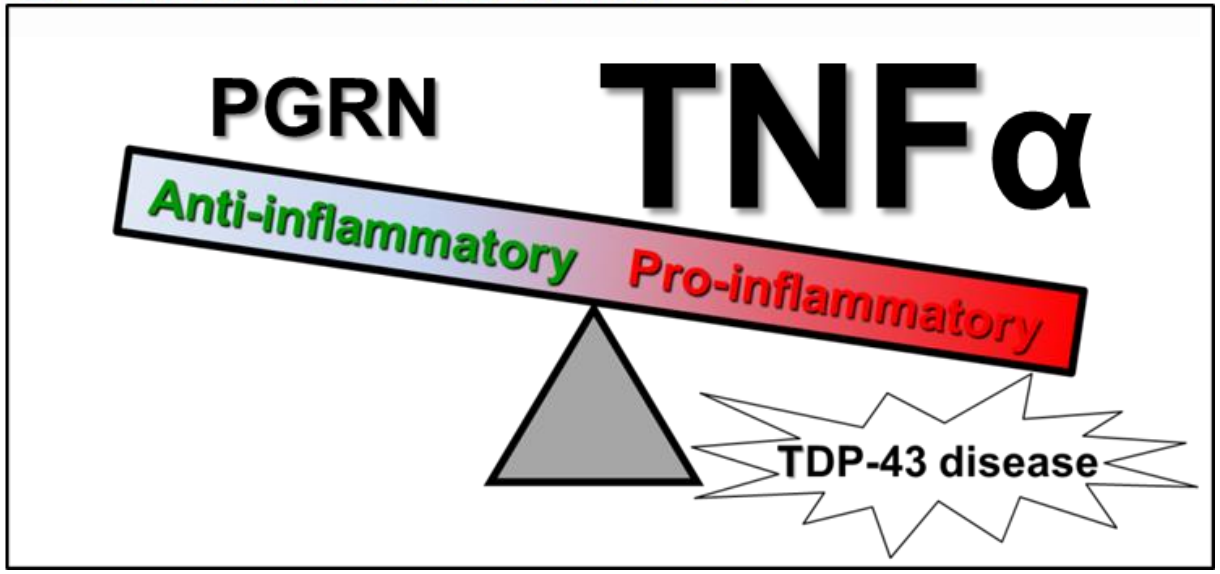


Miller et al., 2013

A. Direct Decrease of PGRN.



B. Direct Increase of TNF-α.



Miller et al., 2013

Autoantibodies to PGRN

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- Rheumatoid Arthritis
- Sarcoidosis
- Sjögren's Syndrome
- Systemic Lupus Erythematosis

2012

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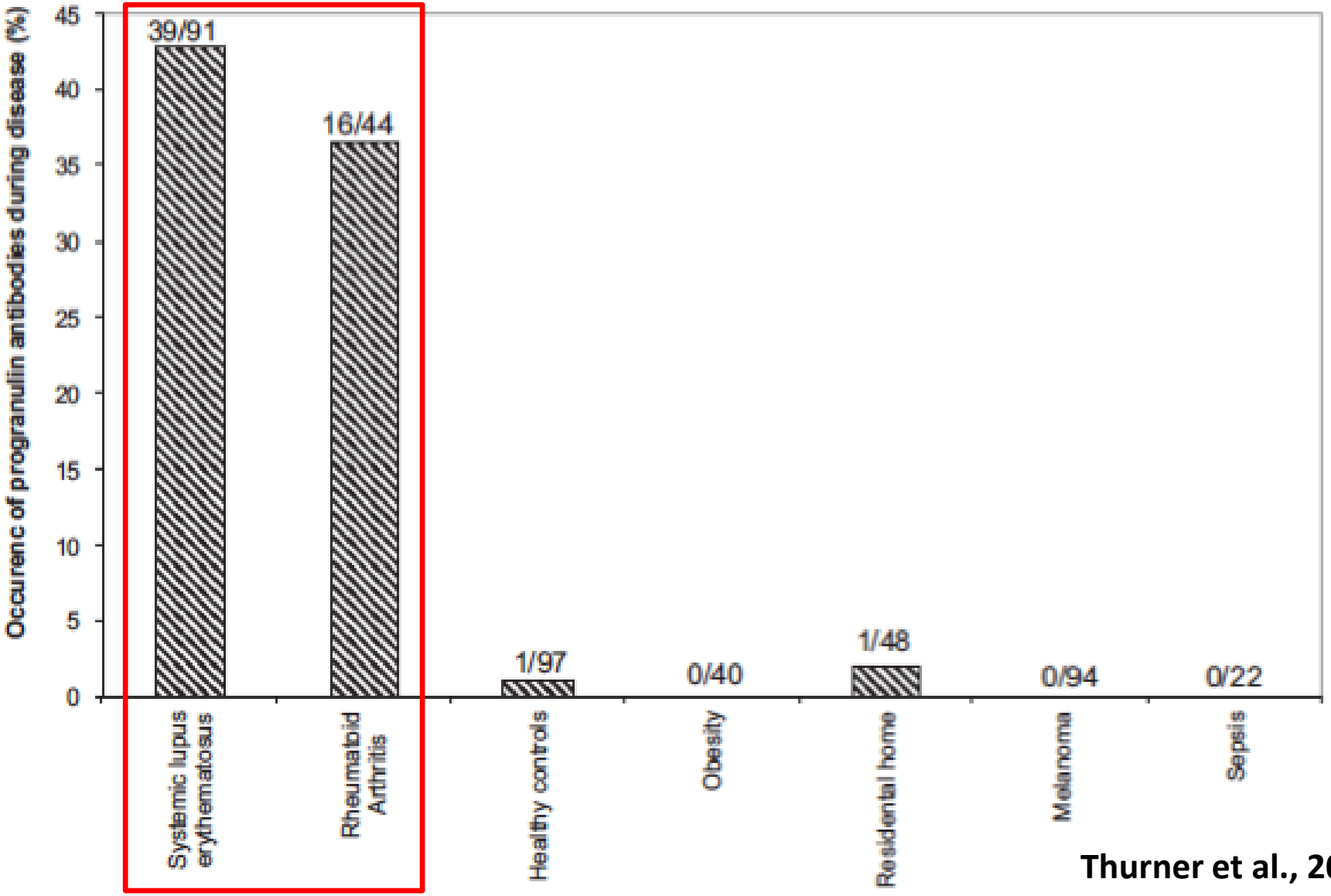
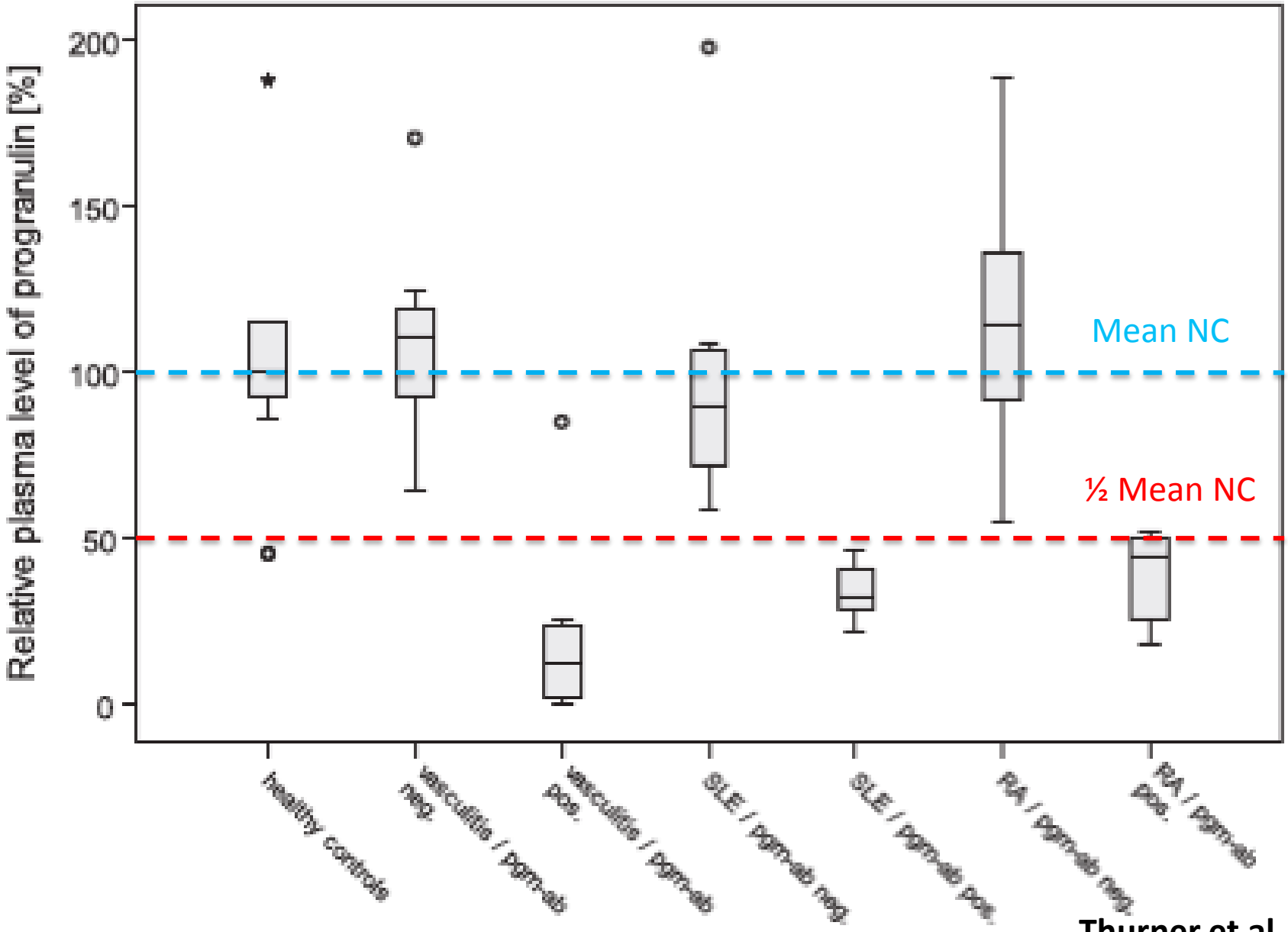
2014

Antibodies to PGRN



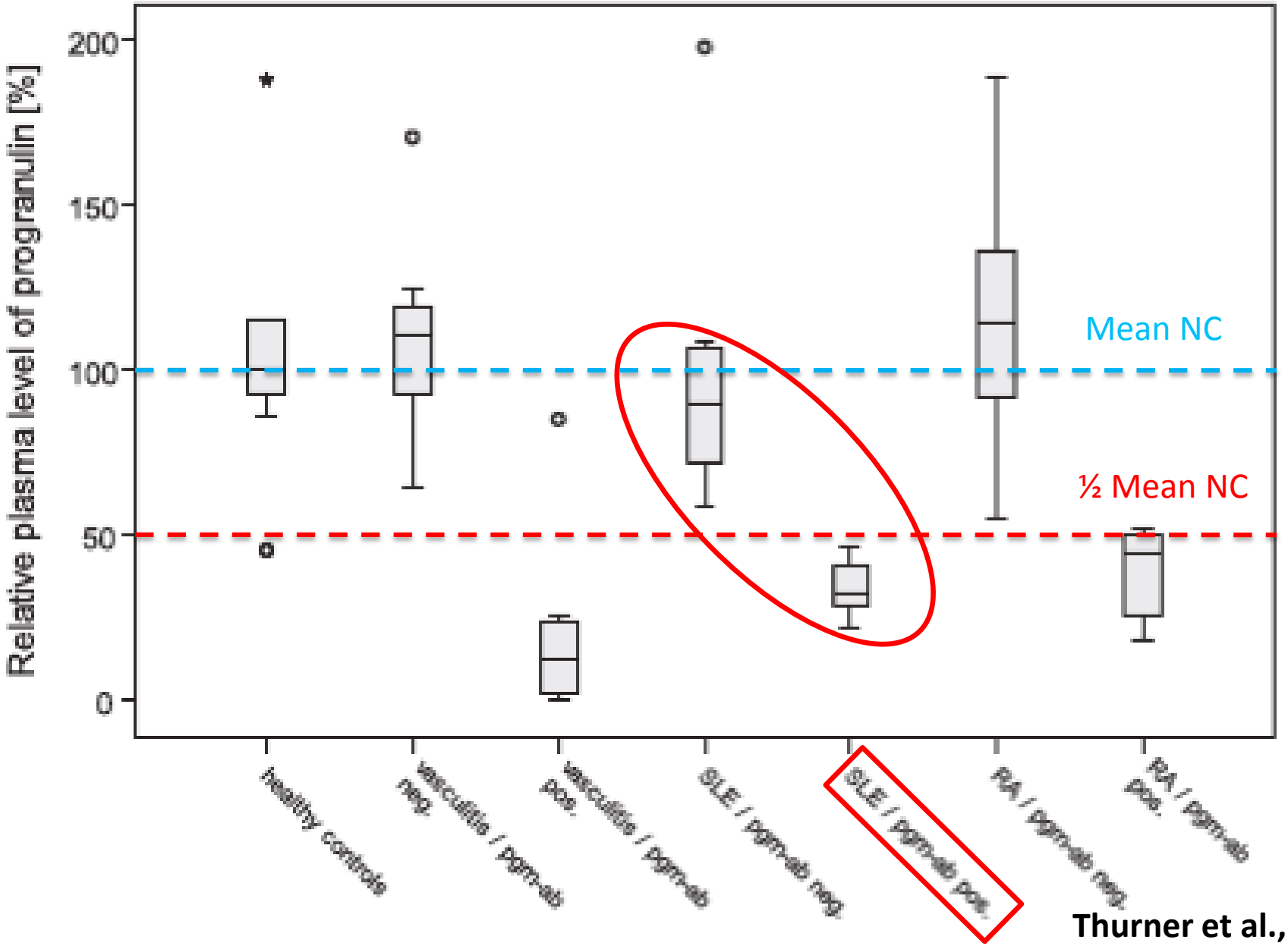
Thurner et al., 2012

Plasma levels of PGRN



Thurner et al., 2012

Neutralizing Effects of PGRN Ab



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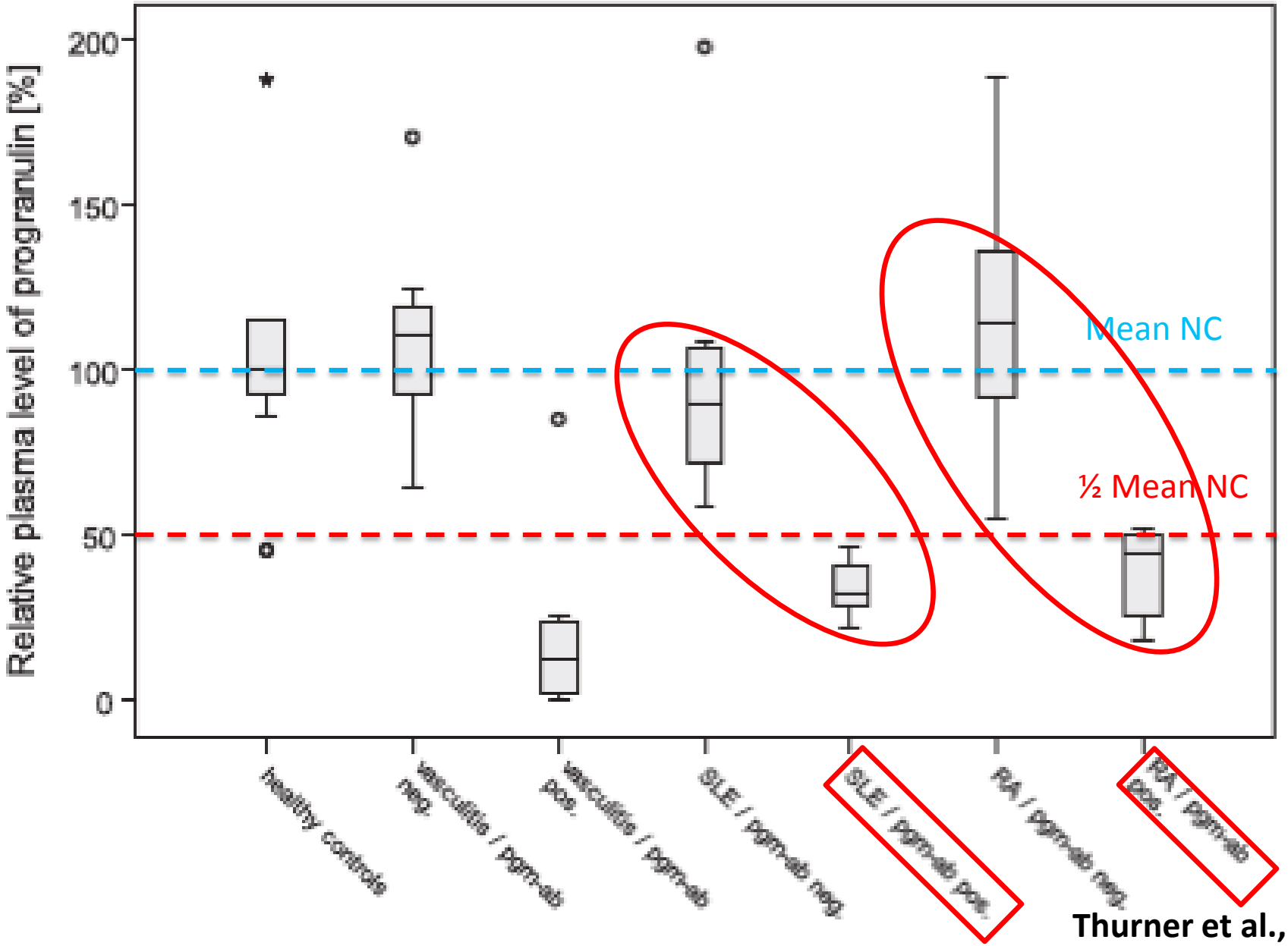

Thurner et al., 2012

Why is PGRN Targeted for Autoantibody Production?

- PGRN expression directly correlated with increasing disease burden in RA, SLE, and Sjögren's

- PGRN is up regulated to fight inflammation, perhaps here it becomes a target for autoantibody production

PGRN may not be the only important protein Targeted for Autoantibody Production

- RAB38 autoantibodies prominently found in vitiligo
- Likely a network of disrupted proteins predispose to vulnerability of FTLD-TDP
- Understanding FTLD-TDP will not only bring potent new insights towards treating neurodegenerative disease…

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- Likely a network of disrupted proteins predispose to vulnerability of FTLD-TDP
- Understanding FTLD-TDP will not only bring potent new insights towards treating neurodegenerative disease… might help bring new insights into treating autoimmune disease!

Conclusions

- AD is more complex than previously believed
  - In order to effectively treat AD it will require targeted strategies towards multiple pathologies
    - Amyloid
    - Tau
    - TDP-43
- FTD provides ideal model systems for developing tau and TDP-43 based theraputics
  - In the process of developing these treatments we will not only help to cure AD but ALS, CTE, and possibly autoimmune disease!

Thanks!

- UCSF Memory & Aging Center
  - Bruce Miller
  - Marilu Gorno-Tempini
  - Adam Boxer
  - Lea Grinberg
  - Kate Rankin
  - Bill Seeley
  - Virginia Sturm
  - Leonel Takada
- Stanford University
  - Tony Wyss-Coray
  - Philip Jaeger
  - Trisha Stan
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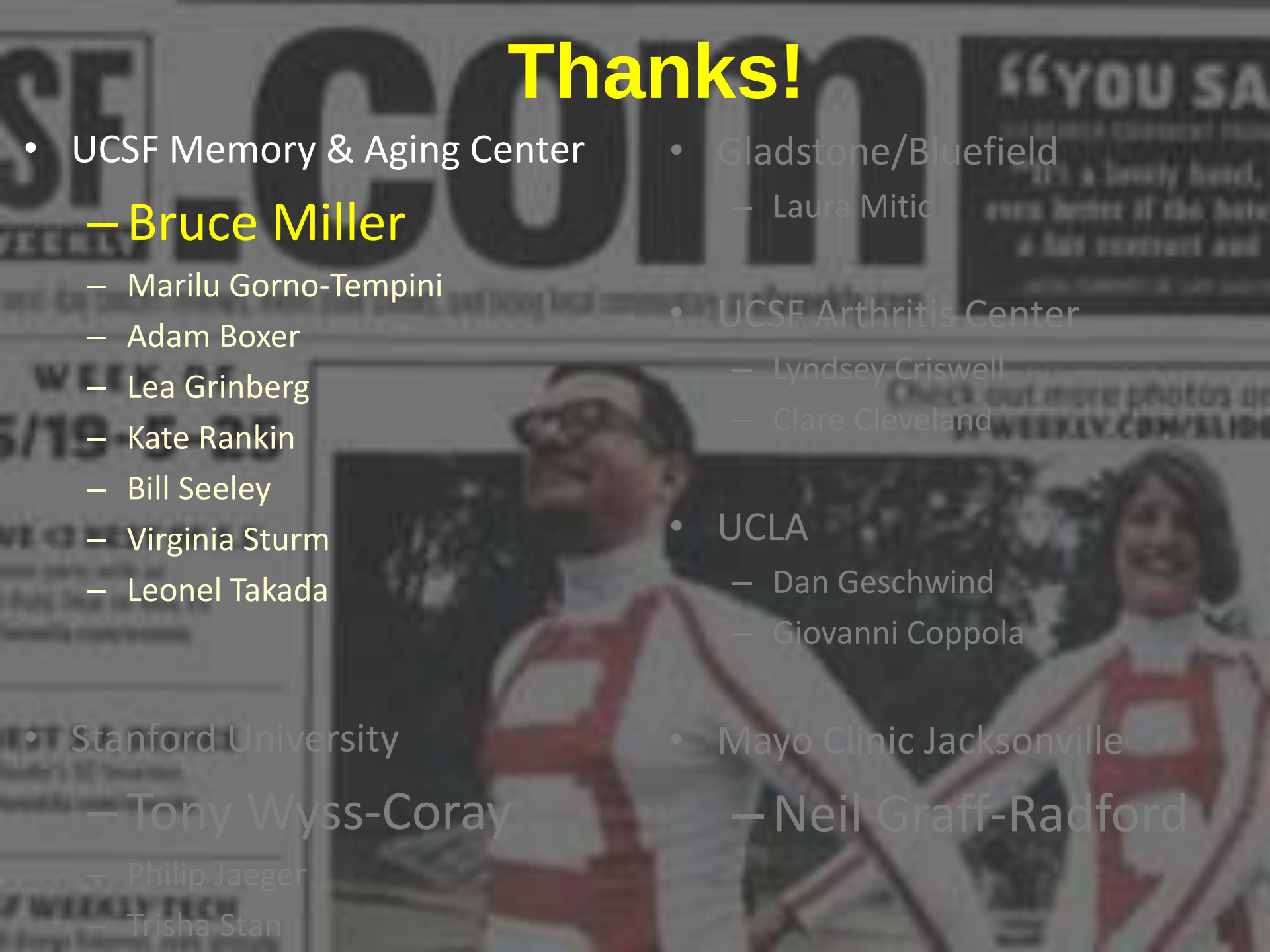
  - Neil Graff-Radford



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