Emerging CSF and serum biomarkers in atypical dementia

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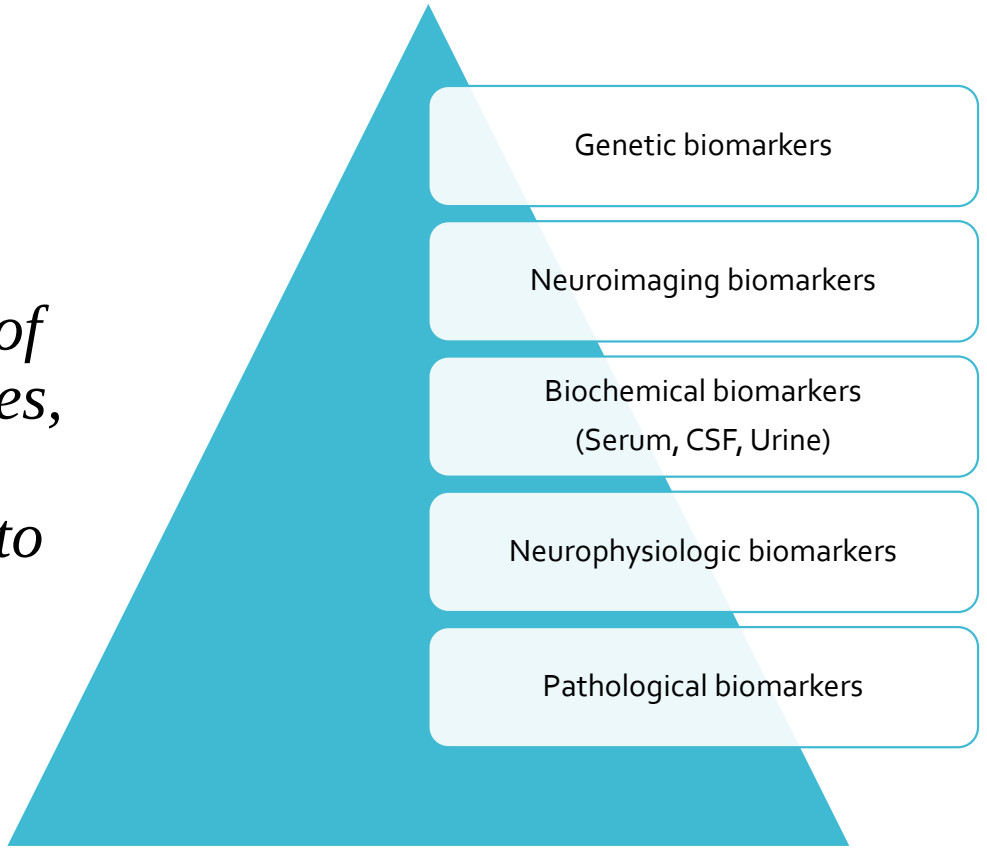
Biomarkers

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.



Clin Pharmacol Ther 69 (3) 89-95

Biomarkers

Ideal biomarker is reproducible, stable over time, widely available and reflects directly the relevant disease process

Diagnostic marker
Progression marker

CSF

Pros

- Less costly and potentially more widely available than amyloid imaging

Cons

- Hampered by the necessity for lumbar puncture
- Problems with standardizing analysis of samples
- Important to collect CSF in tubes made of polypropylene rather than the usual polyethylene, to avoid underestimating amyloid β_{1-42} levels

Blood

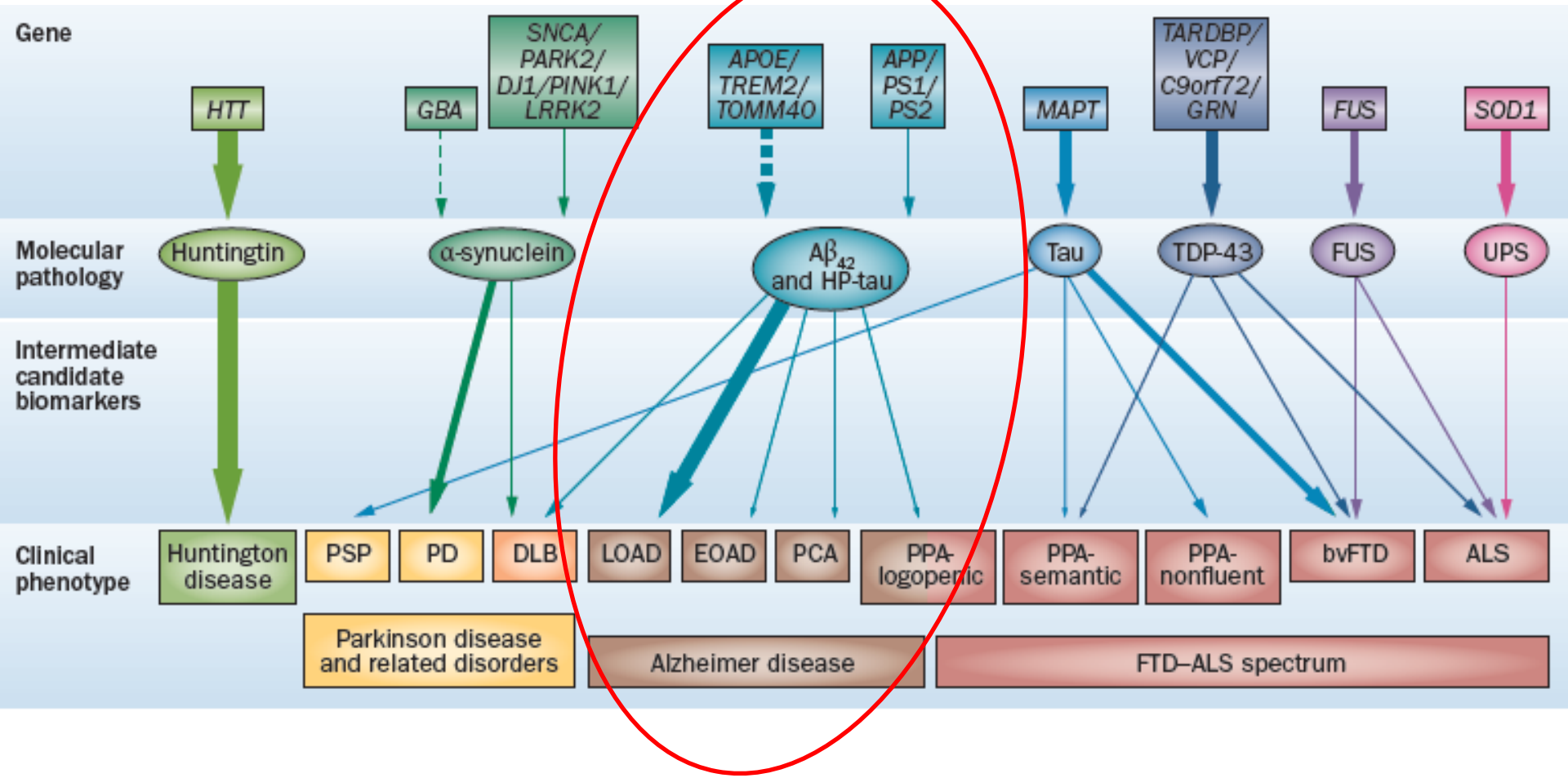
Pros

- Blood analysis has advantages as an approach to population-based disease screening
- Simpler and less invasive

Cons

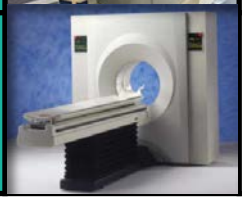
- The blood-brain barrier and the blood-CSF barrier regulate the passage of solutes between blood and the central nervous system (CNS)
- So far with limited success

Neurodegenerative disorders from gene/molecular pathology to clinical phenotype



Pievani, M. et al. Nat. Rev. Neurol. 10, 620–633 (2014)

Core biomarkers of AD

		Amyloid load (A)	Tau pathology (T)	Neurodegeneration (N)	
Fluid	Plasma	Decline $A\beta_{1-42}$	-	Increase t-tau	
	CSF	Decline $A\beta_{1-42}$	Increase p-tau_{181}	Increase t-tau	
Imaging	MRI	-	-	MRI and fMRI	
	PET	Amyloid PET	Tau PET	[^{18}F]FDG	

Def. Biological marker (biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
Clin Pharmacol Ther 69 (3) 89-95

Articles

CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

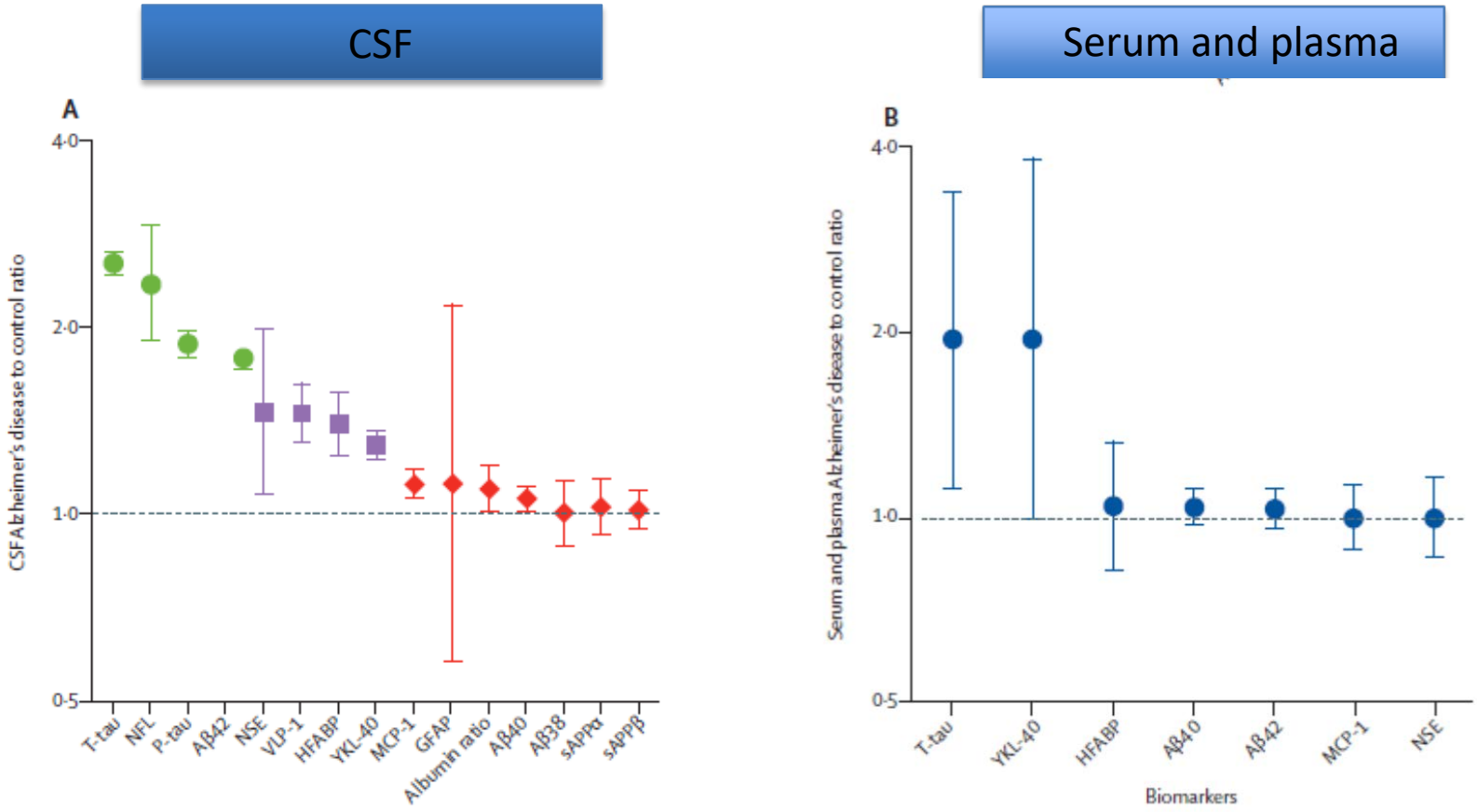
Bob Olsson, Ronald Lautner, Ulf Andreasson, Annika Öhrfelt, Erik Portelius, Maria Bjerke, Mikko Hölttä, Christoffer Rosén, Caroline Olsson, Gabrielle Strobel, Elizabeth Wu, Kelly Dakin, Max Petzold, Kaj Blennow, Henrik Zetterberg

Lancet Neurol 2016; 15: 673–84

Emerging biomarkers of diagnosis AD

- Amyloid precursor protein (APP): Aβ42, Aβ40, Aβ38, and α and β cleaved soluble amyloid precursor protein [sAPPα and sAPPβ]
- Tangle Pathology: P-Tau
- Neurodegeneration: T-tau, Neurofilament light protein [NFL], Neuron-specific enolase [NSE], Visinin-like protein 1 [VILIP-1], and heart fatty acid binding protein [HFABP]
- Glial cell activation: YKL-40, monocyte chemotactic protein 1 [MCP-1], and glial fibrillary acidic protein [GFAP]
- Blood-brain barrier function: CSF to serum albumin ratio

Biomarker performance rating in patients with Alzheimer's disease versus controls



Biomarkers shown in green are significant with good effect sizes, purple significant with moderate effect sizes, red non-significant or significant with minor effect sizes.

Lancet Neurol 2016; 15: 673–84

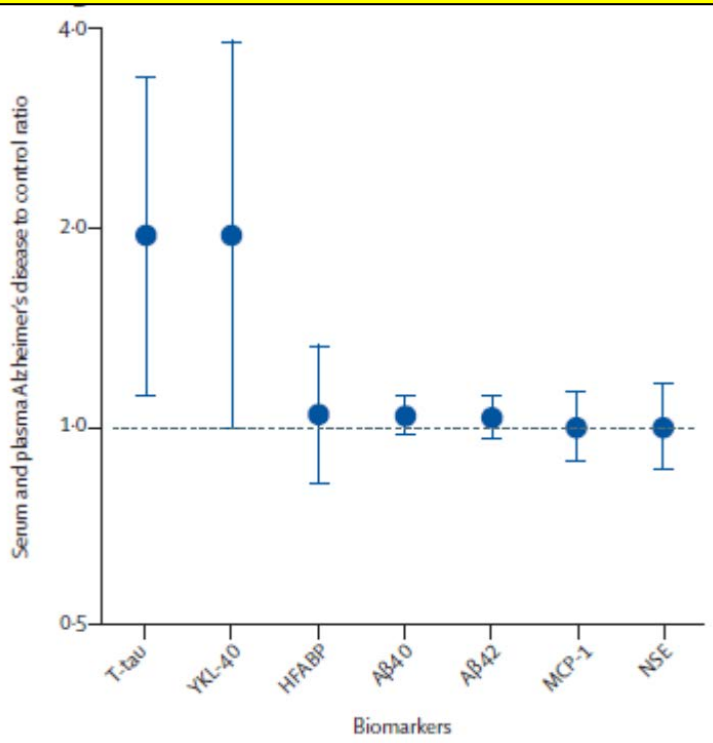
Biomarker performance rating in patients with Alzheimer's

Alzheimer's disease is associated with lower CSF levels of Aβ42 and higher CSF levels of T-tau and P-tau compared with controls. Furthermore, Alzheimer's disease is associated with increased CSF levels of NFL, NSE, VLP-1, HFABP, and YKL-40. and increased plasma levels of T-tau.

No significant differences between plasma or serum concentration of Aβ markers in Alzheimer's disease and controls.

Supporting the hypothesis that plasma Aβ levels reflect peripheral Aβ generation more than they reflect AD brain pathology.

By contrast, plasma levels of T-tau were signifi cantly associated with Alzheimer's disease, more data are needed to verify this association.



Biomarkers shown in green are significant with good effect sizes, purple significant with moderate effect sizes, red non-significant or significant with minor effect sizes.

Lancet Neurol 2016; 15: 673–84

Plasma NfL

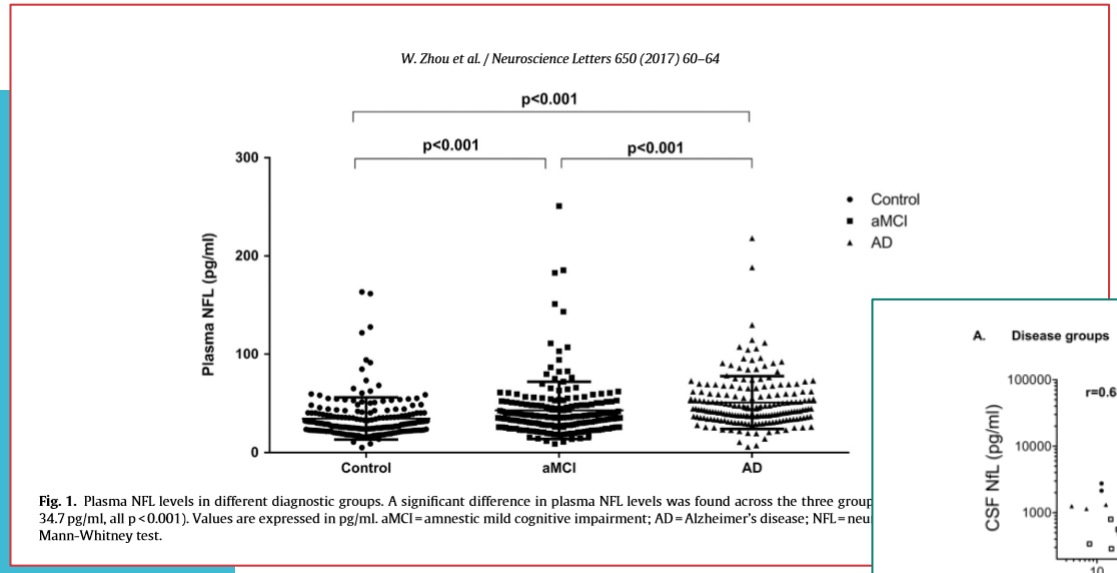


Fig. 1. Plasma NFL levels in different diagnostic groups. A significant difference in plasma NFL levels was found across the three group
34.7 pg/ml, all p < 0.001). Values are expressed in pg/ml. aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease; NFL = neu
Mann-Whitney test.

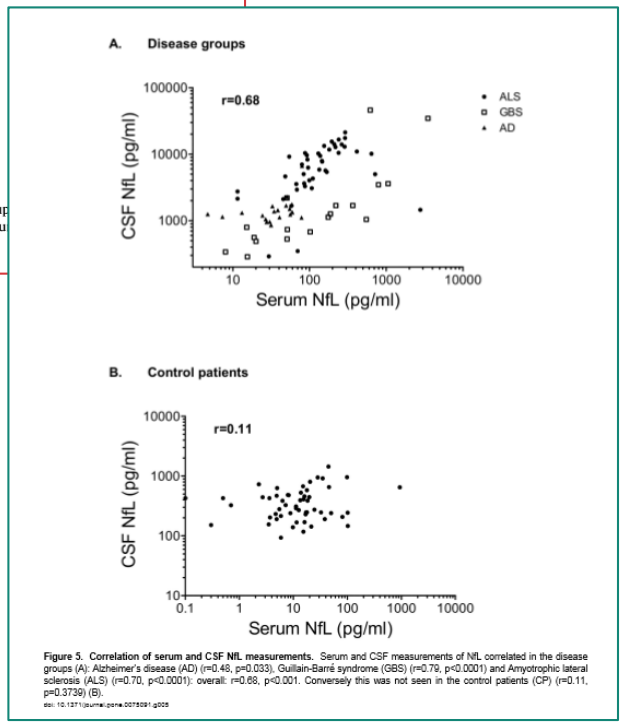


Figure 5. Correlation of serum and CSF NfL measurements. Serum and CSF measurements of NfL correlated in the disease groups (A): Alzheimer's disease (AD) (r=0.48, p=0.033), Guillain-Barré syndrome (GBS) (r=0.79, p<0.0001) and Amyotrophic lateral sclerosis (ALS) (r=0.70, p<0.0001): overall: r=0.68, p<0.001. Conversely this was not seen in the control patients (CP) (r=0.11, p=0.3739) (B).

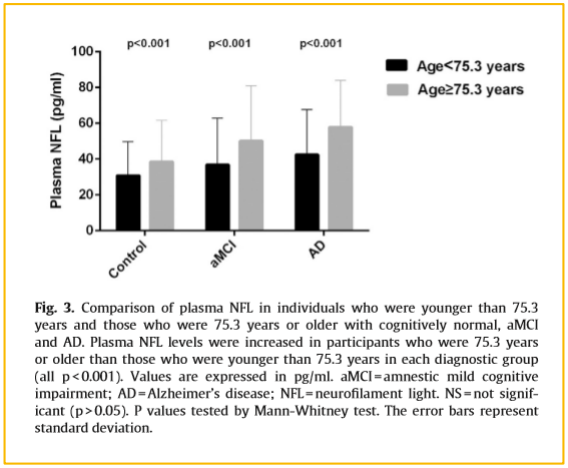


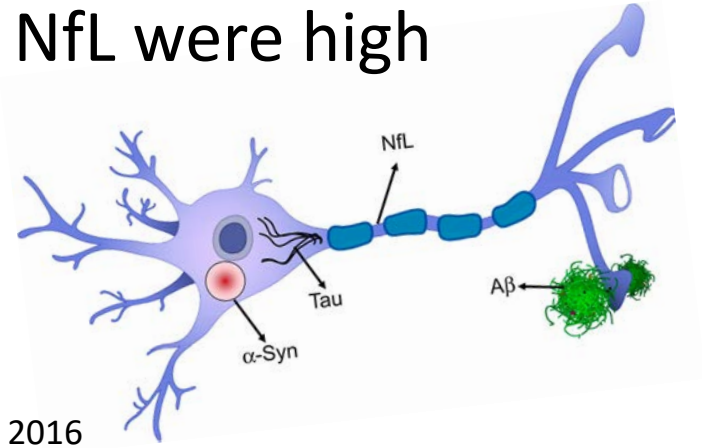
Fig. 3. Comparison of plasma NFL in individuals who were younger than 75.3 years and those who were 75.3 years or older with cognitively normal, aMCI and AD. Plasma NFL levels were increased in participants who were 75.3 years or older than those who were younger than 75.3 years in each diagnostic group (all p < 0.001). Values are expressed in pg/ml. aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease; NFL = neurofilament light. NS = not significant (p > 0.05). P values tested by Mann-Whitney test. The error bars represent standard deviation.

W.Zhou, et al. Neuroscience, 2017

Johanna Gaiottio, et al., PLOS One, Sep 2013

Neurofilaments

- Comprise the neurofilament heavy (NFH), intermediate (NFM) and light (NFL) chain proteins
- Proteins of the axonal cytoskeleton
- Marker of axonal damage
- Increased in ALS, MS, FTD, VaD, etc
- Plasma NfL followed the same pattern; the correlation coefficients with CSF NfL were high



Henrik Zetterberg. Neuron 91, July 6, 2016

CSF/ Plasma NfL in different subtype of FTD

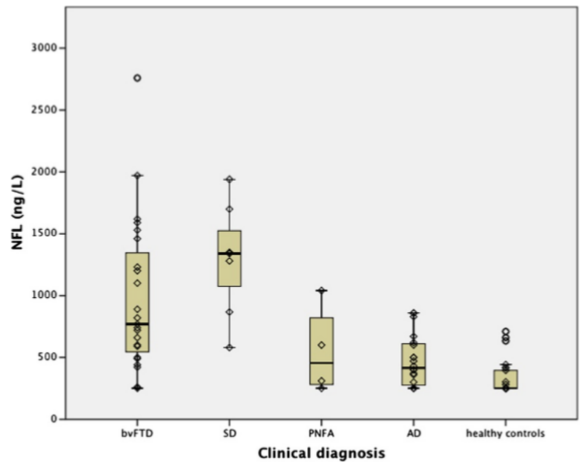
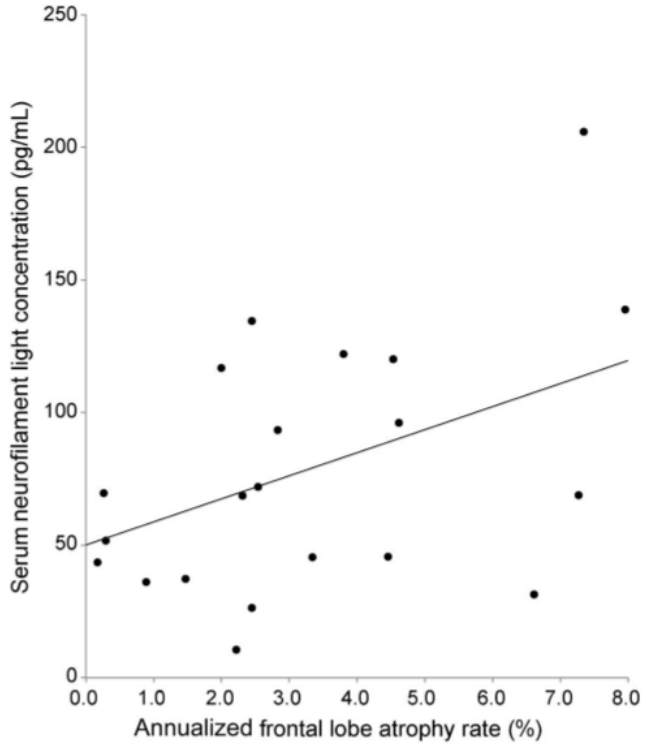


Figure 1 Boxplot with individual values of NFL in each clinical subtype. The number of subjects in each subtype: bvFTD n=23, SD n=7 PNFA n=4, AD n=20, healthy controls n=26. The detection limit of NFL was 250 ng/l.

Landqvist Waldö et al. BMC Neurology 2013, 13:54

Figure 1 Serum neurofilament light chain concentrations in participants by (A)

Figure 2 Relationship of serum neurofilament light chain (NfL) concentrations to frontal lobe atrophy rate

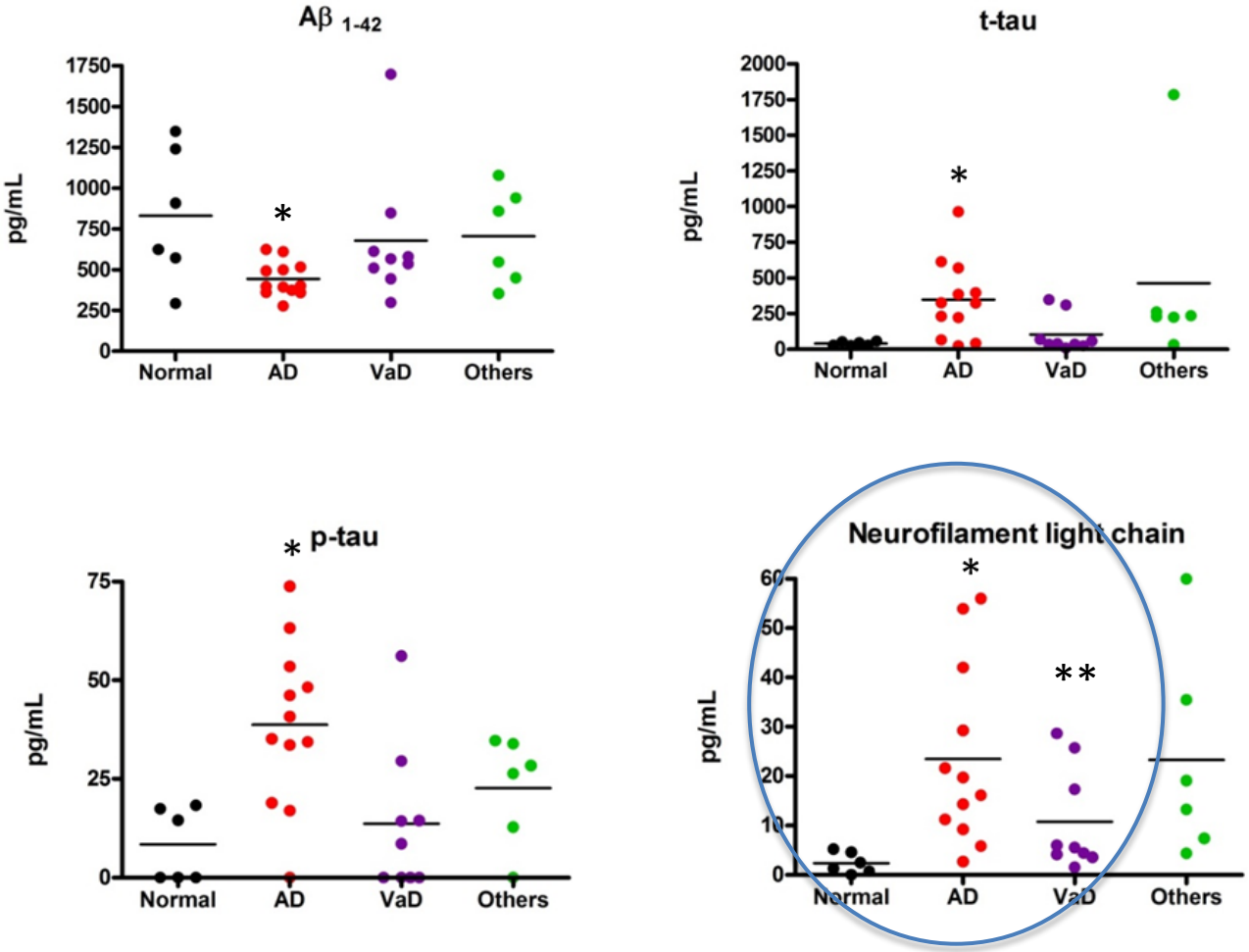


Serum NfL concentrations are correlated with frontal lobe atrophy rates (r = 0.53, p = 0.003). Points indicate individual patient values, and the straight line indicates the line of best fit from a linear regression model of serum NfL on annualized frontal lobe atrophy rate.

All genetic FTD patients have behavioral variant of frontotemporal dementia (bvFTD) except for those *with nonfluent variant of primary progressive aphasia (nfvPPA) and **with primary progressive aphasia not otherwise specified (PPA-NOS). FTD-MND = frontotemporal dementia–motor neuron disease; lvPPA = logopenic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia.

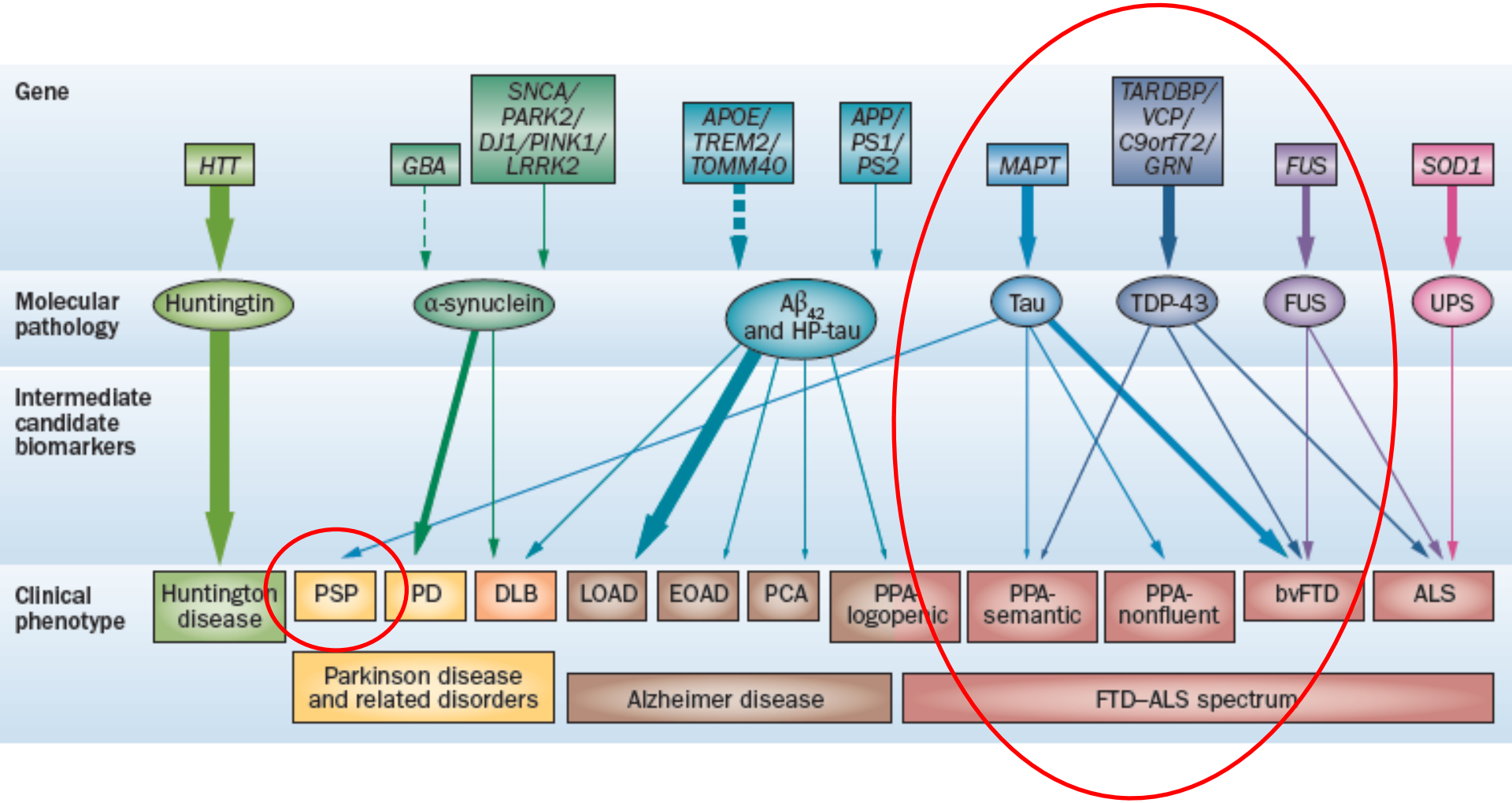
Henrik Zetterberg, et al., Neurology. September 27, 2016

Comparison of CSF biomarkers between Alzheimer's disease, vascular dementia and normal cognitive subject



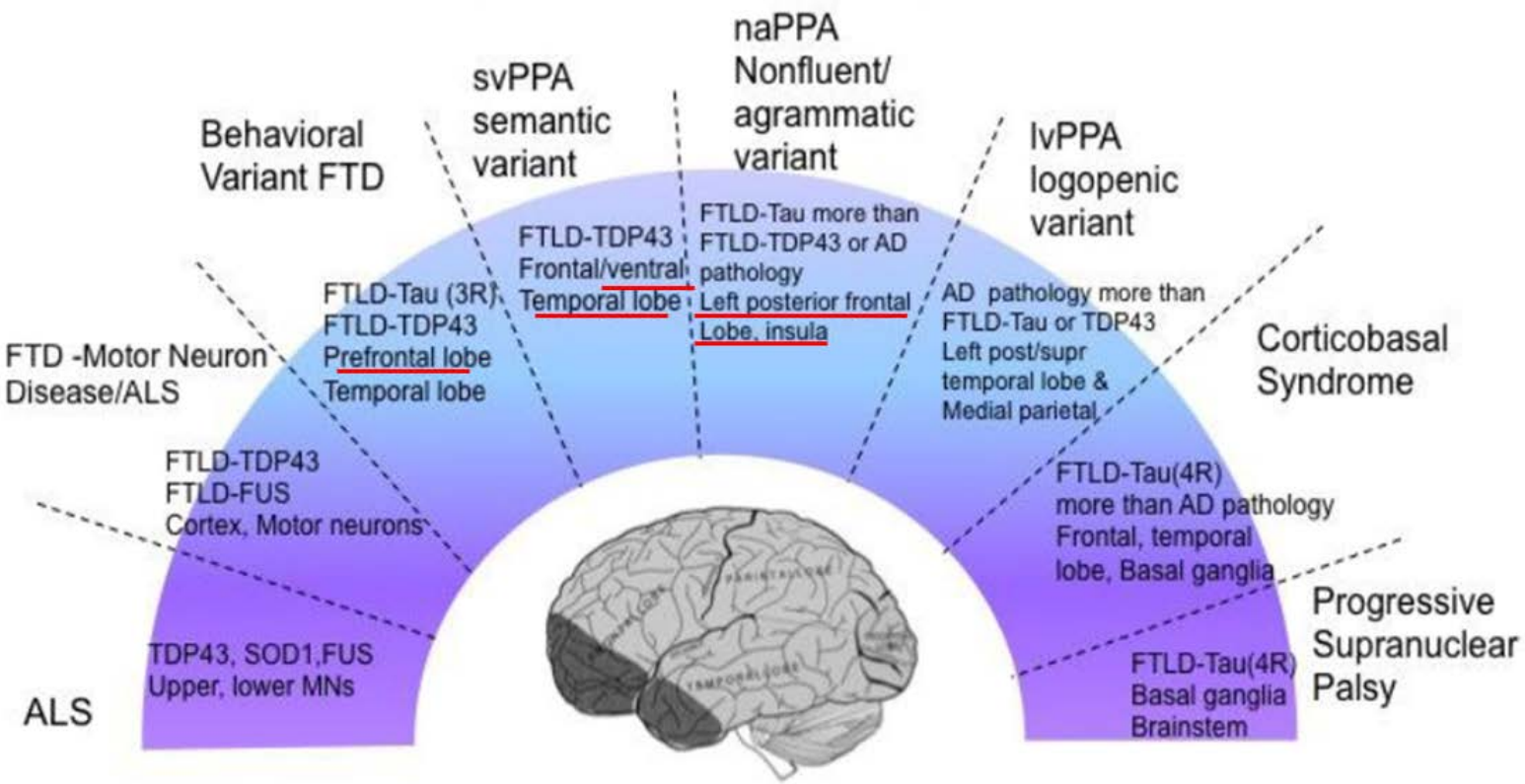
L.Cheewakriengkrai, N. Sirithanakit, in publication

Neurodegenerative disorders from gene/molecular pathology to clinical phenotype



Pievani, M. et al. Nat. Rev. Neurol. 10, 620–633 (2014)

FTLD spectrum



Syndrome: Behavioral variants, Language variants, Motor variants

Promising biomarker candidates for FTLD with evidence from multiple studies

Biomarker (combination)	Alteration	Sensitivity and specificity (%)	References
FTD versus AD			
Ratio Aβ42/pTau181 or pTau181/Aβ42	↓ or ↑ in AD	77–92 and 68–93	(Blasko *et al.* 2006; Kapaki *et al.* 2008; de Souza *et al.* 2011; de Rino *et al.* 2012; Bertoux *et al.* 2014; Scherling *et al.* 2014; Baldeiras *et al.* 2015; Skillbäck *et al.* 2015; Struyfs *et al.* 2015b)
Ratio Aβ42/Tau or Tau/Aβ42	↓ or ↑ in AD	70–95 and 61–97	(Bibl *et al.* 2007b; Bian *et al.* 2008; Kapaki *et al.* 2008; de Souza *et al.* 2011; de Rino *et al.* 2012; Bertoux *et al.* 2014; Scherling *et al.* 2014; Baldeiras *et al.* 2015; Struyfs *et al.* 2015b)
3.5*ln(pTau181)-22.3*ln(Aβ42)-2.0*ln(NfL)	↑ in AD	86 and 100	(de Jong *et al.* 2007)
PSP/CBS versus PD			
NfL	↑ in PSP/CBS	75 and 83	(Holmberg *et al.* 1998, 2001; Constantinescu *et al.* 2010; Bech *et al.* 2012; Hall *et al.* 2012; Bäckström *et al.* 2015; Herbert *et al.* 2015; Magdalinou *et al.* 2015)
FTLD-GRN versus FTLD			
Progranulin (CSF and serum/plasma)	↓ in FTLD-GRN	100 and 100	(Ghidoni *et al.* 2008; Van *et al.* 2008; Philips *et al.* 2010; Schofield *et al.* 2010; Hsiung *et al.* 2011; Almeida *et al.* 2014; Gibbons *et al.* 2015; Feneberg *et al.* 2016)

AD, Alzheimer's disease, CBS, corticobasal syndrome, FTD, frontotemporal dementia, FTLD, frontotemporal lobar degeneration, FTLD-GRN, FTLD with mutation in the *GRN* gene, NfL, neurofilament light chain, PD, Parkinson's disease, PSP, progressive supranuclear palsy.

International Society for Neurochemistry, J. Neurochem. (2016)

Progranulin

- Progranulin is a highly conserved secreted protein that is expressed in multiple cell types, both in the CNS and in peripheral tissues.
- Progranulin has a major role in regulation of lysosomal function and microglial responses in the CNS.
- Regulates cell growth, survival, repair, and inflammation
- Proteolytically processed into peptides called granulins

Progranulin: Functions and neurologic correlations, Neurology, January 2018

Progranulin protein levels are differently regulated in plasma and CSF.Neurology. May, 2014

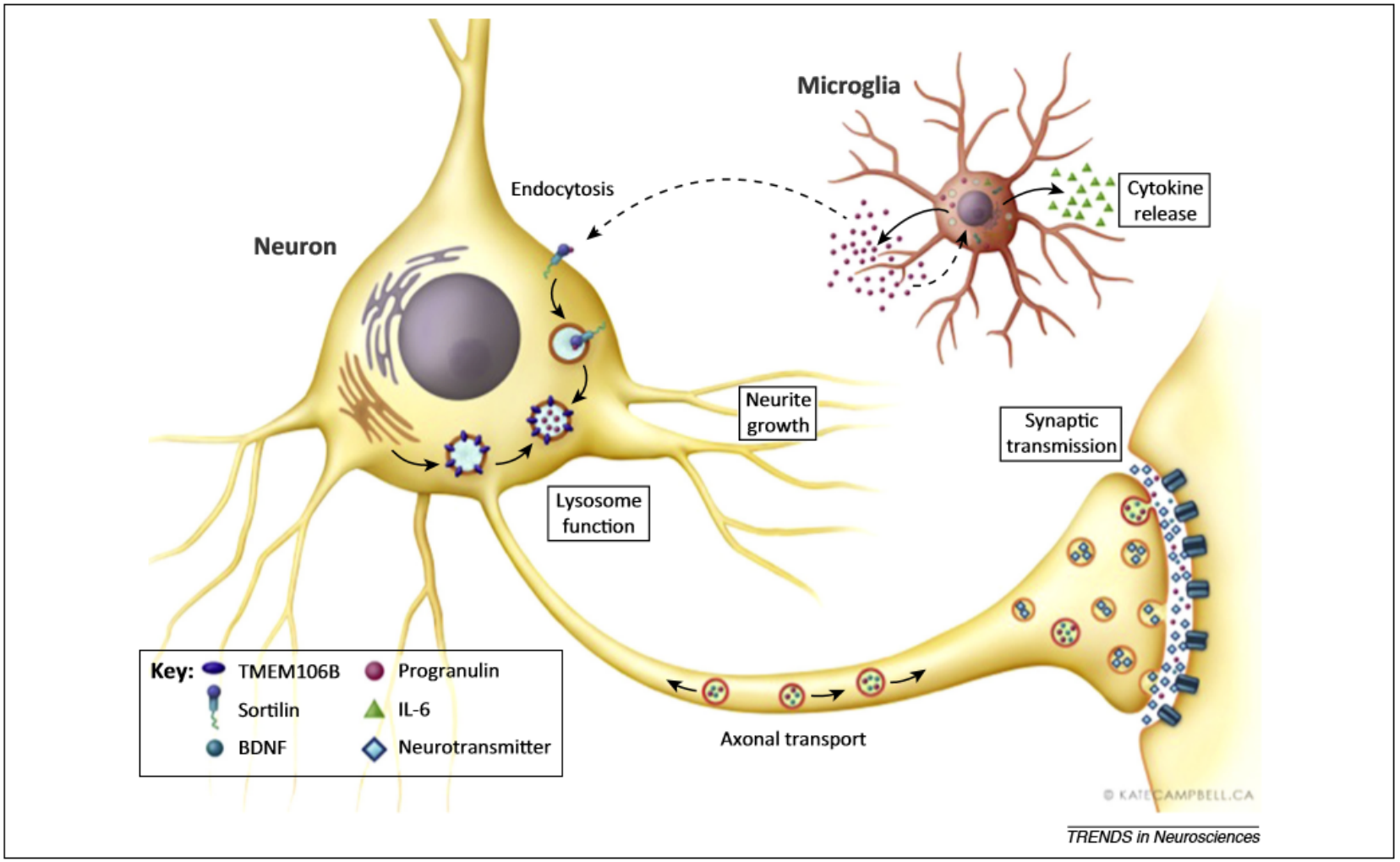


Figure 4. A schematic summarizing the potential functions of progranulin in the brain. In neurons, progranulin co-localizes in late endosomes and early lysosomes with the transmembrane protein TMEM106B [32–34]. Progranulin also co-localizes with markers of large dense-core vesicles, such as brain-derived neurotrophic factor (BDNF), that undergo both anterograde and retrograde transport along axons [101]. At synaptic and extra-synaptic sites, progranulin is secreted in an activity-dependent manner, similar to BDNF, and influences synapse structure and function [86,88,101]. Extracellular progranulin can be endocytosed through the sortilin receptor and delivered to lysosomes, where it is rapidly degraded [98,99]. The absence of progranulin in neurons reduces neurite outgrowth, which is mediated by extracellular progranulin [84,85,87,88,100]. In microglia, progranulin is constitutively expressed and secreted [80,106]. Whether secreted progranulin acts cell-autonomously, non-cell autonomously, or both is not known. The absence of progranulin in microglia causes increased production and release of multiple cytokines, such as interleukin-6 (IL-6; shown), in response to an inflammatory stimulus [80,106]. Broken arrows represent hypothetical interactions.

Trends in Neurosciences. July 2014

Progranulin

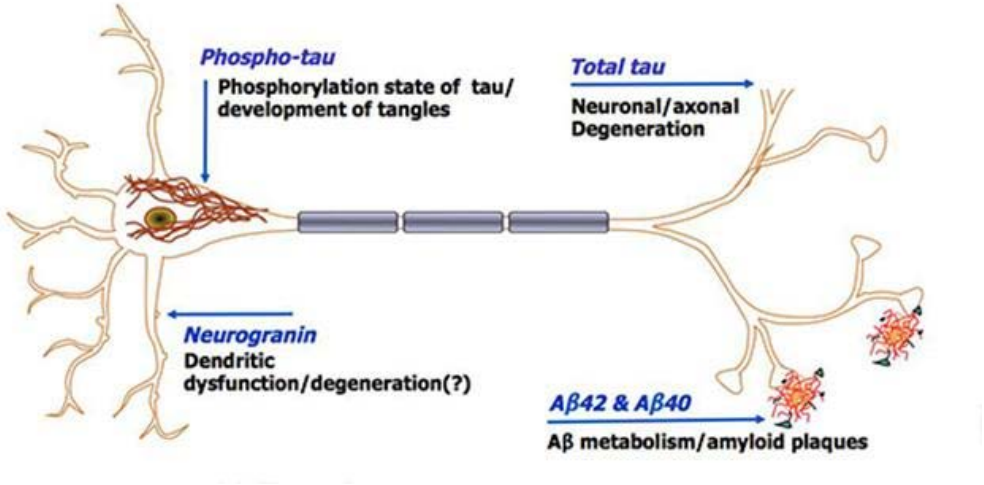
- Pathologic GRN mutations reduce progranulin levels or result in loss of function.
- PGRN ELISA were successful in predicting *GRN* mutation status in serum, plasma, and CSF of patients with FTLD.
- PGRN levels are vary greatly
- No correlation between serum and CSF
- Need more studies to determine the sensitivity and specificity

New biomarker candidates

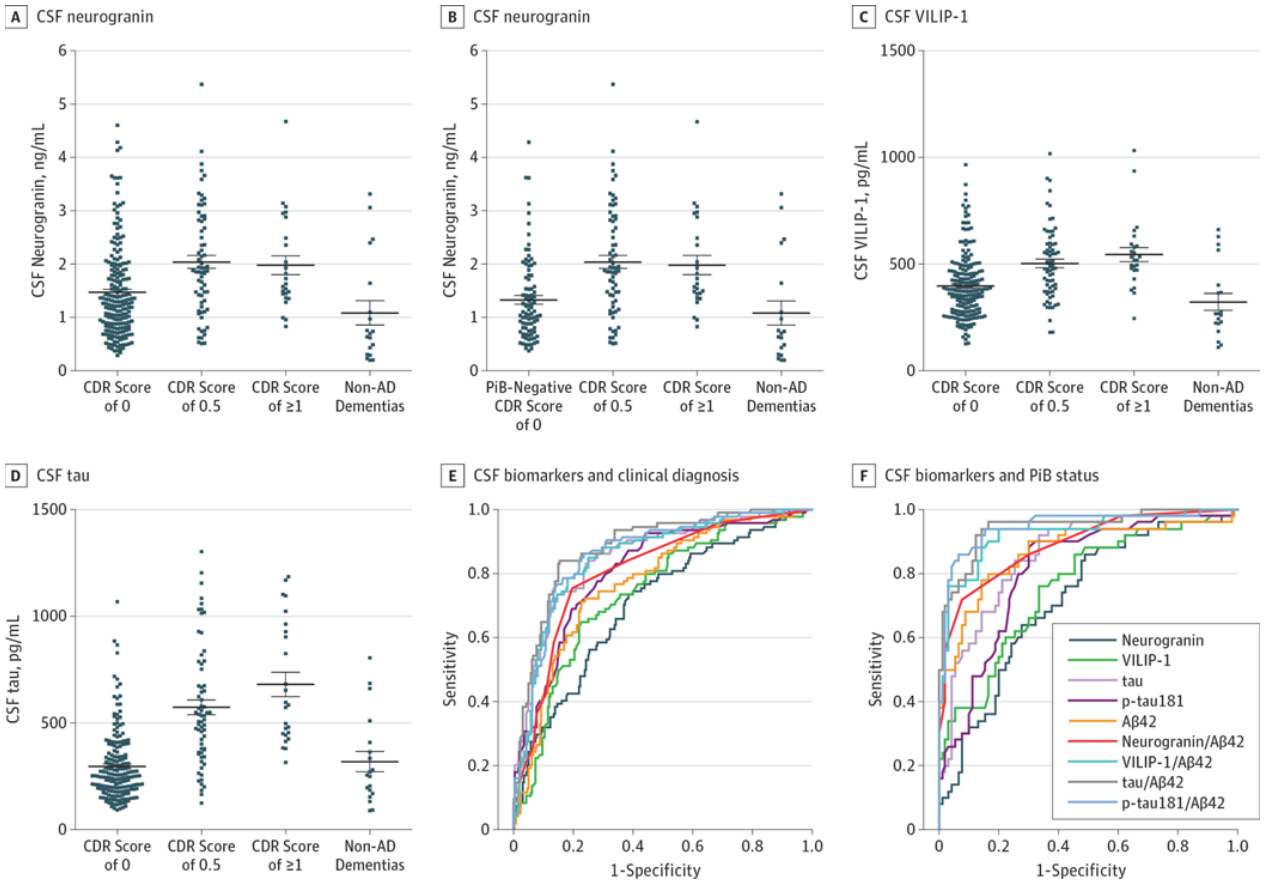
Biomarker (combination)	Alteration	References
FTD versus AD		
Ratio endostatin/Aβ42	↑ in AD	(Salza *et al.* 2015)
Neurogranin	↑ in AD	(Janelidze *et al.* 2016)
FTD versus DLB/PDD		
NfL	↑ in FTD	(Skillbäck *et al.* 2014)
GFAP	↑ in FTD	(Ishiki *et al.* 2016)
PSP/CBS versus PD		
sAPPα	↑ in PD	(Magdalinou *et al.* 2015)
sAPPβ	↑ in PD	(Magdalinou *et al.* 2015)
FTLD-Tau versus FTLD-TDP		
Ratio pTau181/Tau	↑ in FTLD-Tau	(Hu *et al.* 2013; Borroni *et al.* 2015)

International Society for Neurochemistry, J. Neurochem. (2016)

Neurogranin



- Calmodulin-binding postsynaptic neuronal protein that is abundantly expressed in perikaryal and dendritic cytoplasm (post synaptic protein)
- Neurodegenerative marker: synaptic plasticity and learning



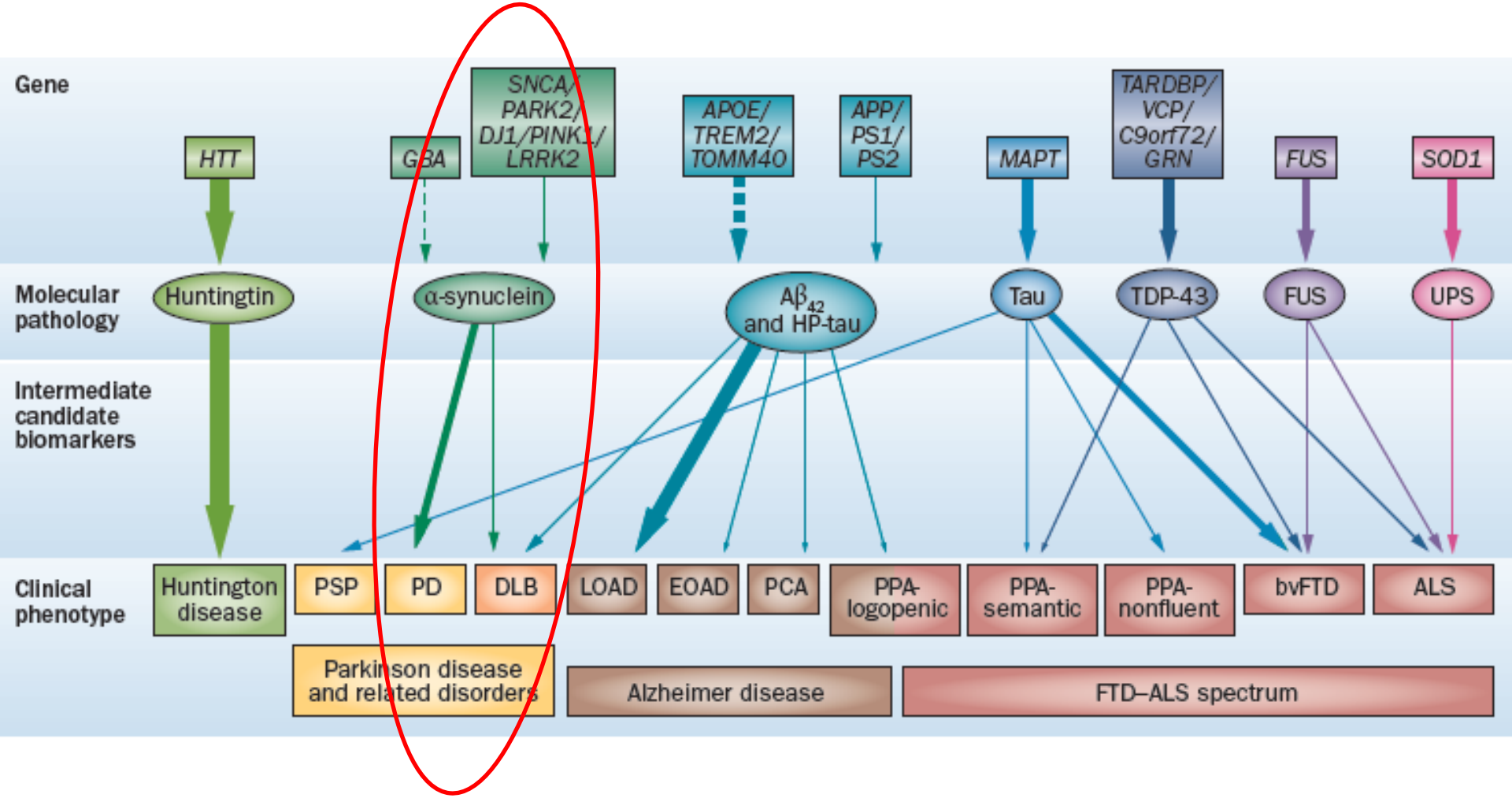
Scatterplots of Cerebrospinal Fluid (CSF) Biomarker Levels by Clinical Diagnosis and Clinical Dementia Rating (CDR)

The JAMA Network

From: **Diagnostic and Prognostic Utility of the Synaptic Marker Neurogranin in Alzheimer Disease**

JAMA Neurol. 2016;73(5):561-571. doi:10.1001/jamaneurol.2016.0086

Neurodegenerative disorders from gene/molecular pathology to clinical phenotype



Pievani, M. et al. Nat. Rev. Neurol. 10, 620–633 (2014)

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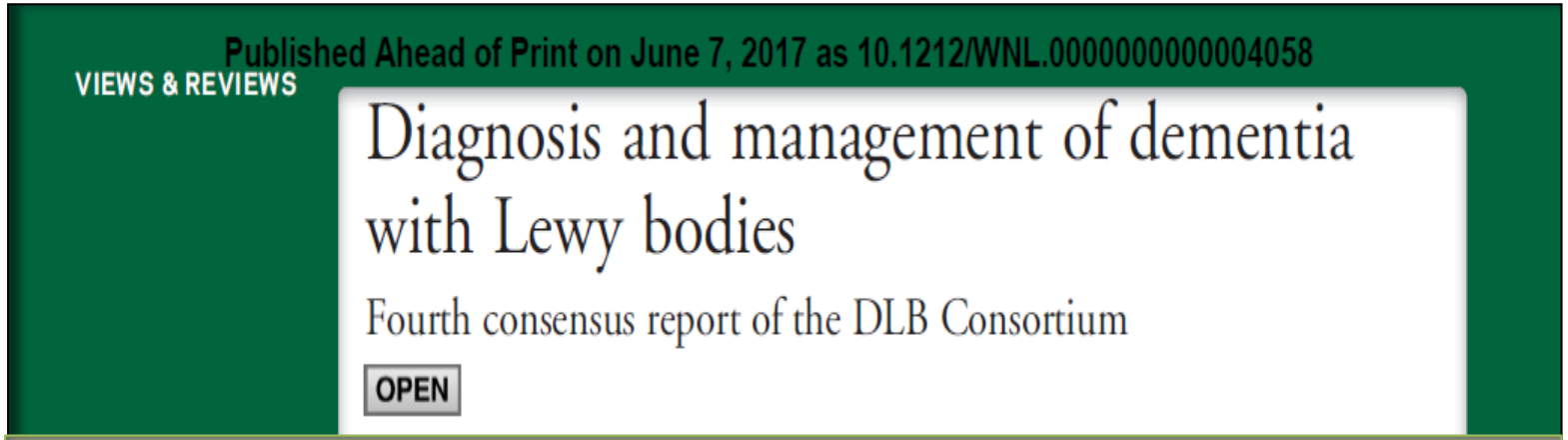

New revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies

Ian G. Mckeith.el al., Neurology. July 4 2017

AD CSF biomarkers

- $A\beta_{42}$ values were significantly lower in AD patients than in PD patients (with or without dementia) but showed no difference with DLB
- T-tau and p-tau are lower in DLB
- CSF p-tau may be a good marker for differentiation between AD and DLB

Neurol Sci (2001) 22:77-78

Journal of Neurological Sciences. Volume 345, 15 October 2014

CSF α - synuclein

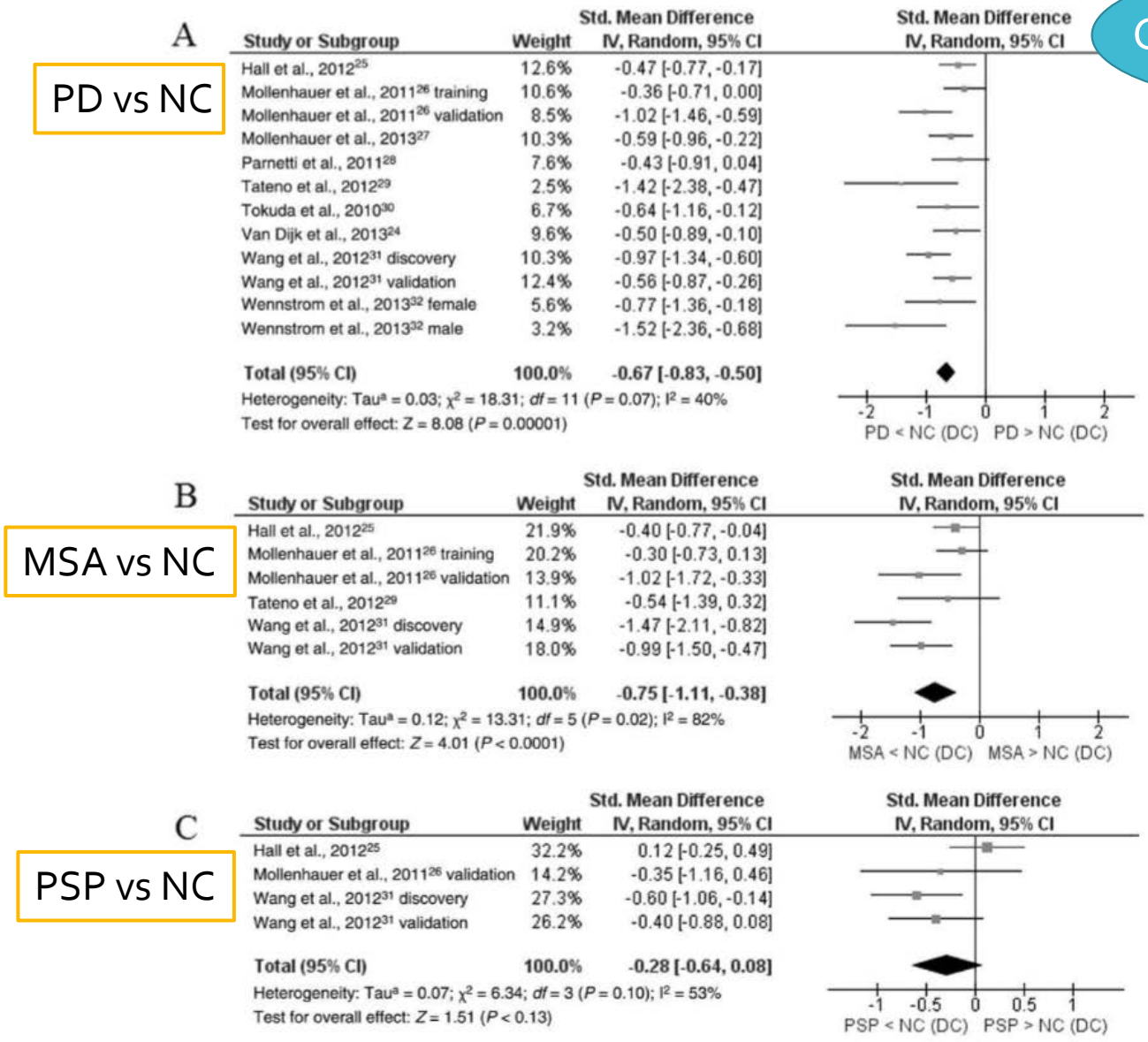

FIG. 1. Forest plot of standardized mean difference (SMD) of alpha-synuclein concentration in Parkinson's disease (PD) and atypical parkinsonism. (**A**) PD showed a significantly lower level of alpha-synuclein in cerebrospinal fluid (CSF) than controls. The included studies were heterogeneous. (**B**) Alpha-synuclein in multiple system atrophy was more reduced than controls with heterogeneous studies. (**C**) In contrast, there was no significant difference of alpha-synuclein concentration between progressive supranuclear palsy and controls. The included studies were heterogeneous.

Movement disorder, May 2014

CSF α - synuclein

Table 1: Studies on quantification of α-synuclein level in CSF of patients with DLB and other synucleinopathies.

Level of total α-synuclein	Study	Blood contamination was considered*	Controls		Synucleinopathies				Results
			Healthy controls	Neurological controls	AD	Lewy body diseases			
						DLB	PD	MSA	
	Tokuda et al. [31]	No	9	29	—	—	33	—	PD patients showed significantly lower α-syn level than the controls ($P < 0.0001$). The level of α-syn decreased significantly with age ($P = 0.0076$) and correlated to inversely assigned Hoehn and Yahr stage ($P < 0.0001$).
	Mollenhauer et al. [28]	No	—	13	13	38	8	—	The level of α-syn in DLB and PD patients were lower than AD patients and controls ($P = 0.025$).
	Kasuga et al. [32]	No	—	21	31	34	—	—	The level of α-syn in DLB patients was significantly lower than those in patients with AD ($P < 0.05$) and other dementias ($P < 0.01$). In DLB patients, reduced α-syn level correlated with the lower level of CSF Aβ42 ($P = 0.01$). Patients with *SNCA* duplication showed a decrease of CSF α-syn.
↓	Tokuda et al. [44]	No	16	12	—	—	32	—	The level of total α-syn was lower in PD patients than in age-matched controls. The level of α-syn oligomers was significantly higher in PD patients than in age-matched controls.
	Mollenhauer et al. [34]	Yes	— —	76 20	62 3	55 66	51 273	29 15	Upper and lower rows indicate training and validation cohorts, respectively. The level of α-syn was significantly lower in DLB, PD, and MSA patients than in other neurological diseases.
	Hong et al. [33]	Yes	92	—	38	—	86	20	The level of α-syn was decreased in PD and MSA patients.
	Parnetti et al. [37]	Yes	—	32	48	32	38	—	The level of α-syn was lower in patients with neurodegenerative diseases than in cognitively normal subjects, but the level of α-syn alone did not distinguish synucleinopathies from tauopathies. An inverse correlation between α-syn and total tau levels was observed ($P < 0.01$).
	Tateno et al. [36]	No	—	11	9	6	11	11	The levels of α-syn of DLB, PD, and MSA were lower than AD.
	Wennstrom et al. [38]	No	24	—	26	18	—	—	The level of α-syn in female DLB patients was lower than AD ($P = 0.041$) patients and controls ($P = 0.028$).

International Journal of Alzheimer's Disease, 2012

CSF α - synuclein

Table 1: Continued.

Level of total α-synuclein	Study	Blood contamination was considered*	Controls		AD	Synucleinopathies			Results
			Healthy controls	Neurological controls		Lewy body diseases			
						DLB	PD	MSA	
	Öhrfelt et al. [45]	Yes	55	—	66	15	15	—	PD, DLB patients and controls showed comparable levels of α-syn. AD patients showed significantly lower level of α-syn than the controls ($P < 0.001$). AD patients with MMSE scores below 20 had significantly lower level of α-syn than AD patients with MMSE scores of 20 or higher ($P = 0.02$).
	Noguchi-Shinohara et al. [46]	No	—	—	21	16	—	—	The level of α-syn did not differ between DLB and AD patients. In DLB patients, the duration of illness was associated with lower level of α-syn ($P < 0.05$).
	Spies et al. [47]	No	57	—	131	40	—	—	The level of α-syn was comparable between DLB, AD, and controls. The level of α-syn decreased with age ($P = 0.001$).
→	Reesink et al. [48]	Yes	34	—	63	35	18	—	The level of α-syn was not different among PD, DLB, AD, and controls. In DLB patients, lower α-syn was related to lower MMSE scores ($P < 0.05$) and worse category fluency ($P < 0.05$).
	Aerts et al. [49]	Yes	57	—	—	3	58	47	The level of α-syn was comparable among PD, MSA, DLB patients and controls. In PD group, the level of α-syn was negatively correlated with age at time of lumber puncture ($P < 0.006$).
	Foulds et al. [50]	Yes	20	—	—	16	38	8	The level of total α-syn was not different between PD, DLB, MSA and control groups. Oligomeric phosphorylated α-syn was significantly high in patients with MSA ($P < 0.001$).
	Park et al. [51]	No	18	11	—	—	23	—	The level of total α-syn in PD patients was comparable to that of control groups. The level of α-syn oligomer in PD patients was significantly higher than controls ($P = 0.005$).

Arrows indicate decreased (↓) and comparable (→) levels α-synuclein. Sample numbers are shown in each category. *Erythrocyte counts or haemoglobin levels were considered as a confounding factor. AD: Alzheimer's disease; DLB: dementia with Lewy bodies; PD: Parkinson's disease; MSA: multiple system atrophy; α-syn: α-synuclein; MMSE: minimental state examination.

International Journal of Alzheimer's Disease, 2012

CSF alpha-synuclein Meta analysis compare DLB vs AD

Study or Subgroup	DLB Mean	DLB SD	DLB Total	AD Mean	AD SD	AD Total	Weight	Mean Difference IV, Random, 95% CI
Kasuga 2010	8.2	4.2	34	12.2	5.8	31	0.7%	-4.00 [-6.48, -1.52]
Mollenhauer 2008	3.8	3.3	38	6.2	4.2	13	0.7%	-2.40 [-4.91, 0.11]
Mollenhauer 2011a	1.42	1.26	55	1.85	1.47	62	12.2%	-0.43 [-0.92, 0.06]
Mollenhauer 2011c	0.3	0.2	13	0.8	0.9	21	15.9%	-0.50 [-0.90, -0.10]
Noguchi-Shinohara 2009	44.7	24.9	16	49.3	44.5	21	0.0%	-4.60 [-27.21, 18.01]
Parnetti 2008	18.1	16	32	34.8	54	48	0.0%	-16.70 [-32.95, -0.45]
Spies 2009	38	29	40	37	36.1	131	0.0%	1.00 [-9.91, 11.91]
Tateno 2011	0.0976	0.0581	6	0.1841	0.0711	9	36.6%	-0.09 [-0.15, -0.02]
Wennstrom 2012	0.378	0.166	18	0.464	0.233	26	33.9%	-0.09 [-0.20, 0.03]
Total (95% CI)			**252**			**362**	**100.0%**	**-0.24 [-0.45, -0.03]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 22.66$, df = 8 (P = 0.004); $I^2 = 65\%$

Test for overall effect: Z = 2.24 (P = 0.02)

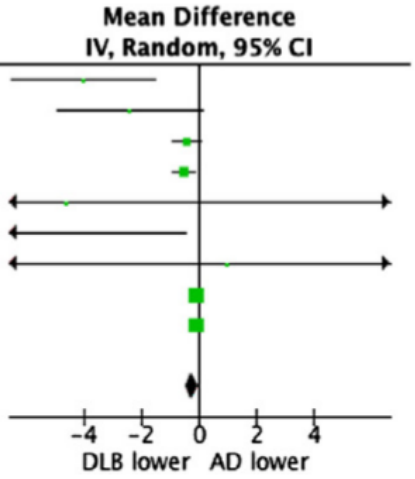

Fig. 2. Forest plot comparing mean CSF alpha-synuclein concentrations of DLB vs AD patients.

High sensitivity but low specificity

Table 3: Studies of quantification of α-synuclein level in blood of patients with DLB and other synucleinopathies.

	Methods	Samples*	Results**
El-Agnaf et al. [57]	ELISA	Plasma Cont (27), PD/DLB (34)	α-Synuclein oligomers were elevated in patients with PD/DLB compared to controls.
Lee et al. [58]	ELISA	Plasma Cont (51), PD (105), MSA (38)	The α-synuclein level was increased in patients with PD (79.9 pg/mL) and in those with MSA (78.1 pg/mL) compared with controls (76.1 pg/mL). The α-synuclein level was significantly higher in patients with PD than in those with MSA.
Duran et al. [59]	ELISA	Plasma Cont (60), PD (95)	The α-synuclein level was elevated in patients with PD compared to healthy controls. Antiparkinsonian treatment does not change plasma α-synuclein level.
Foulds et al. [60]	ELISA	Plasma (not described)	The level of phosphorylated α-synuclein was higher in patients with PD than healthy controls. None of the levels of total α-synuclein, oligomeric α-synuclein, or oligomeric phospohorylated α-synuclein was different between PD patients and controls.
Shi et al. [61]	Bead-based flow cytometric assay	Plasma Cont (95), AD (33), PD (117)	No significant difference was found among patients with PD (36.8 ng/mL), AD (32.4 ng/mL), and those with healthy controls (39.5 ng/mL).
Park et al. [51]	ELISA	Plasma Cont (29), PD(23)	There was no difference in oligomeric and total α-synuclein in plasma between PD patients and controls.
Li et al. [62]	IP-Western blot	Plasma Cont (11), PD (27)	The α-synuclein level was significantly lower in patients with PD than in those with age-matched healthy controls. Early-onset PD patients had lower α-synuclein levels than late-onset PD patients.
Laske et al. [63]	ELISA	Serum Cont (40), AD (80), DLB (40)	The α-synuclein level was significantly lower in patients with DLB (4.7 ng/mL) than in those with AD (7.0 ng/mL) and healthy controls (8.1 ng/mL).

Summary biomarkers for DLB

Table 13.1
Summary of reported candidates of biochemical biomarkers for the diagnosis of DLB and differential diagnosis between DLB and AD and surrogate biomarkers for PD

	CSF biomarkers	Plasma/serum biomarkers
DLB	A-syn↓	Heart-type FABPs↑
	(A-syn oligomers? ↑in PD)	EGF↓
	Neurosin↓	
	Oxidized Aβ1-40↑	
	HVA, 5-HIAA, MHPG↓	
DLB vs. AD	Aβ1-42 (AD < DLB)	Heart-type FABPs (AD < DLB)
		t-tau, p-tau (AD > DLB)
PD	A-syn (to monitor disease severity)	EGF (to predict cognitive decline)
	Aβ1-42, p-tau (to predict prognosis)	
	A-syn oligomers (to predict prognosis)	

DLB dementia with Lewy bodies, *A-syn* α-synuclein, *PD* Parkinson's disease, *FABPs* fatty acid-binding proteins, *EGF* epidermal growth factor, *HVA* homovanillic acid, *5-HIAA* 5-hydroxyindoleacetic acid, *MHPG* 3-methoxy-4-hydroxyphenylethyleneglycol, *AD* Alzheimer's disease, *t-tau* total tau, *p-tau* phosphorylated tau

Tokuda T.,et al., Alpha-Synuclein in Cerebrospinal Fluid. Dementia with Lewy Bodies. Springer, 2017 Tokyo

Vascular dementia

Table 1 Cerebrospinal fluid (CSF) biomarkers with high diagnostic utility: (Biomarker levels in CSF are raised in vascular dementia, VaD).

Biomarkers	Diagnostic utility
CSF:serum albumin ratio, CSF total protein	To identify blood–brain barrier damage to the small intravascular vessels
Sulfatide	To identify demyelination of white matter
Neurofilament	To identify axonal degeneration (marker of white matter damage)
Matrix metalloproteases	To identify changes in the extracellular matrix associated with cardiovascular disease (i.e. vascular disease with inflammation)
Serum to CSF Folate ratio	Low ratio in VaD
Increased total tau, p-tau, decreased amyloid β42	May differentiate VaD from Alzheimer's disease and other NDD (Neurodegenerative Diseases)

Biomarkers in vascular dementia. Biomarkers and genomic medicine, 2015.

Vascular dementia

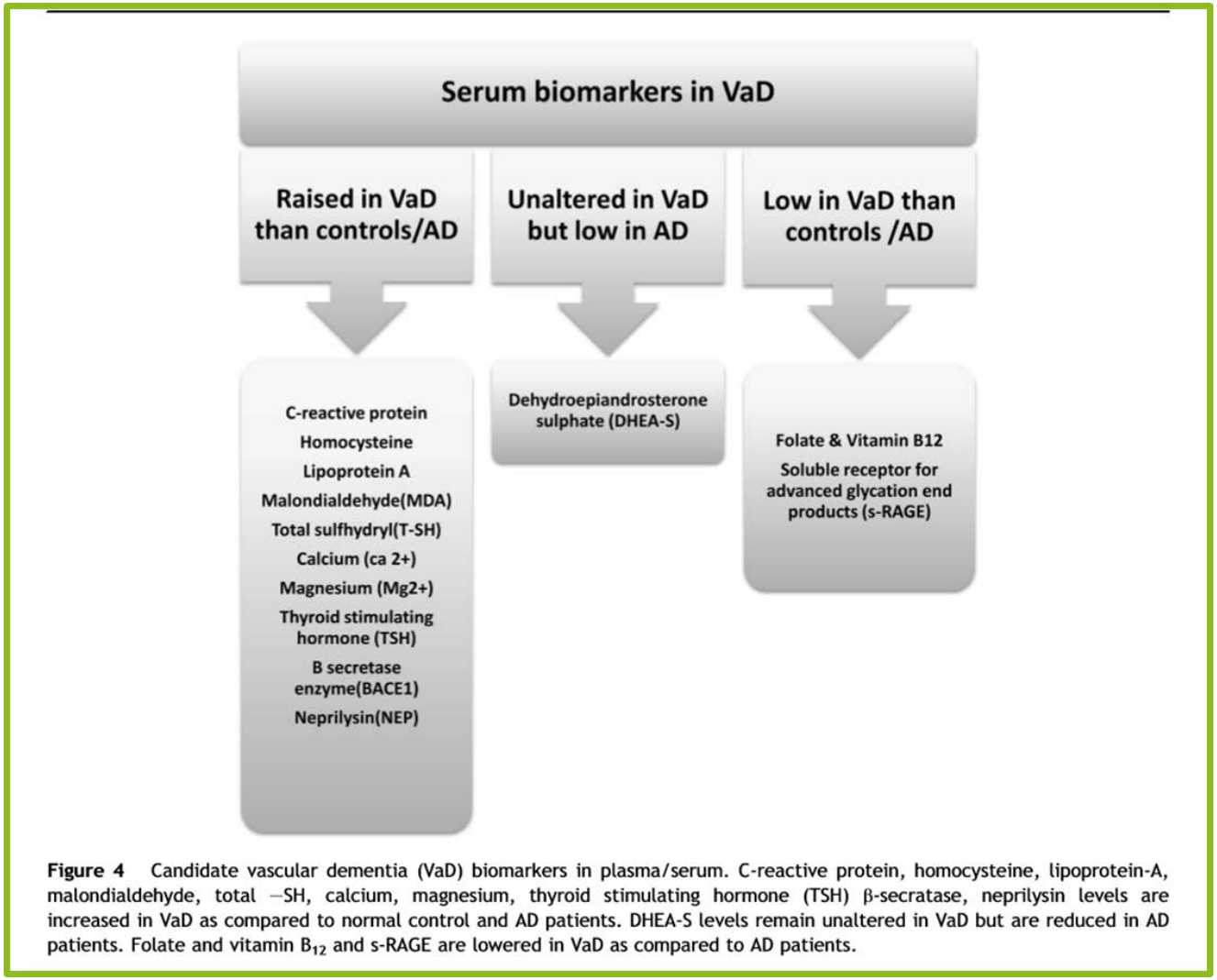

Figure 4 Candidate vascular dementia (VaD) biomarkers in plasma/serum. C-reactive protein, homocysteine, lipoprotein-A, malondialdehyde, total −SH, calcium, magnesium, thyroid stimulating hormone (TSH) β-secratase, neprilysin levels are increased in VaD as compared to normal control and AD patients. DHEA-S levels remain unaltered in VaD but are reduced in AD patients. Folate and vitamin B_{12} and s-RAGE are lowered in VaD as compared to AD patients.

Biomarkers in vascular dementia. Biomarkers and genomic medicine, 2015.

Principle biomarkers and expression levels in the CSF in dementia

	AD	MCI	FTD	sCJD	LBD	VaD
	Biomarkers related to pathogenic processes in dementia					
Tau	↑	↑	↑/-	↑↑	-	↑/-
p-Tau	↑	↑	-	↑	-	-
Aβ42	↓↓↓	↓/-	↓/-	↓	↓↓	↓/-
Aβ40	-	-	-	↓	-	-
Aβoligomers	↑	↑	NA	NA	NA	NA
α-synuclein	↑/-	-	-	↑	↓	↓
Prion protein	↓/-	NA	NA	↓	↓	NA
14 - 3- 3	-	-	-	↑	-	-
	Alternative biomarkers					
mtDNA	↓	NA	-	-	NA	NA
NF-L	↑	↑	↑↑	↑	↑	↑
GAP-43	↑	NA	-	NA	NA	-

Adapt from Neurology; 2012:78:47-54, Neurobiology; 2016: 138-140

Conclusions

- Biochemical biomarkers are potentially more widely available than amyloid imaging
- Not ideally biomarker
- Currently acknowledged that AD core CSF biomarkers can discriminate AD from other dementia/NC, but it is hard to diagnose an individual patient only by measuring the value of single marker
- Many potential biomarkers are coming but need more researches