# Conference: Mechanisms of Neurodegeneration in Human Prion Diseases and Their Intersection with AD/ADRD

November 12 - 14, 2024

Bethesda Marriott
5151 Pooks Hill Road
Bethesda, MD 20814

**11:00 am - 12:00 pm: Neuropathologic overlap of prion diseases and ADRDs: Potential for cross-seeding**

- Moderator: **Gabor G. Kovacs MD, PhD,** Professor, Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
- **Bernardino Ghetti, MD,** Distinguished Professor, Indiana University School of Medicine, Indianapolis, IN
- **Rodrigo Morales, PhD,** Professor, The George and Cynthia W Mitchell Center for Alzheimer's Disease and Other Brain Related Illnesses, Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX

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Neurodegeneration in Human Prion Diseases
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# CURRENT CONCEPTS OF MIXED PATHOLOGIES IN NEURODEGENERATIVE DISEASES

2

GABOR G. KOVACS MD PhD FRCPC

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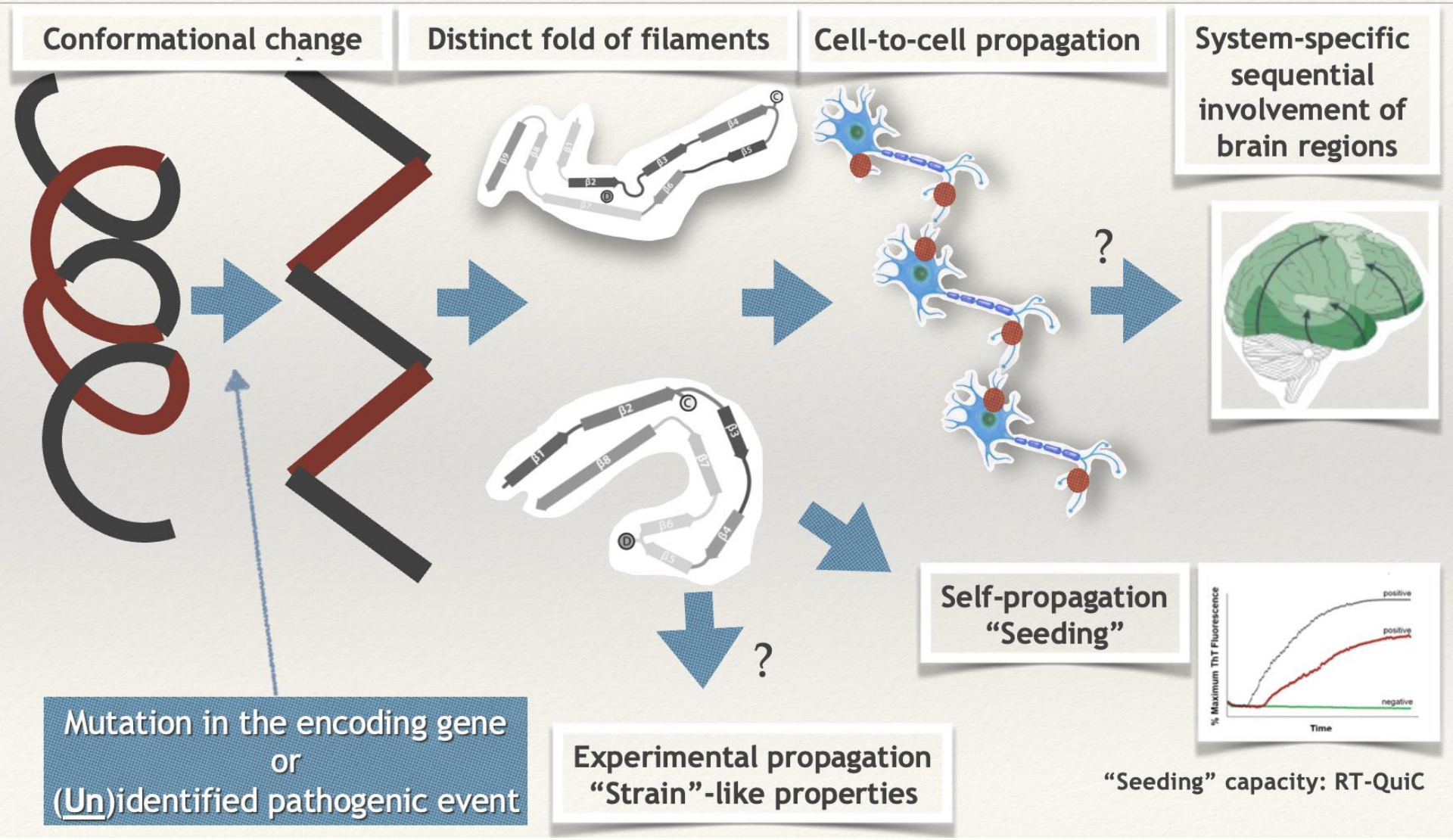
Consultant Neuropathologist, Laboratory Medicine Program, University Health Network;

Principal Investigator, UofT Tanz Centre for Research in Neurodegenerative Disease (CRND), Krembil Brain Institute;

Faculty/Neurologist, Edmond J. Safra Program in Parkinson's Disease and Co-Director Rossy Program for PSP research

# Protein misfolding diseases



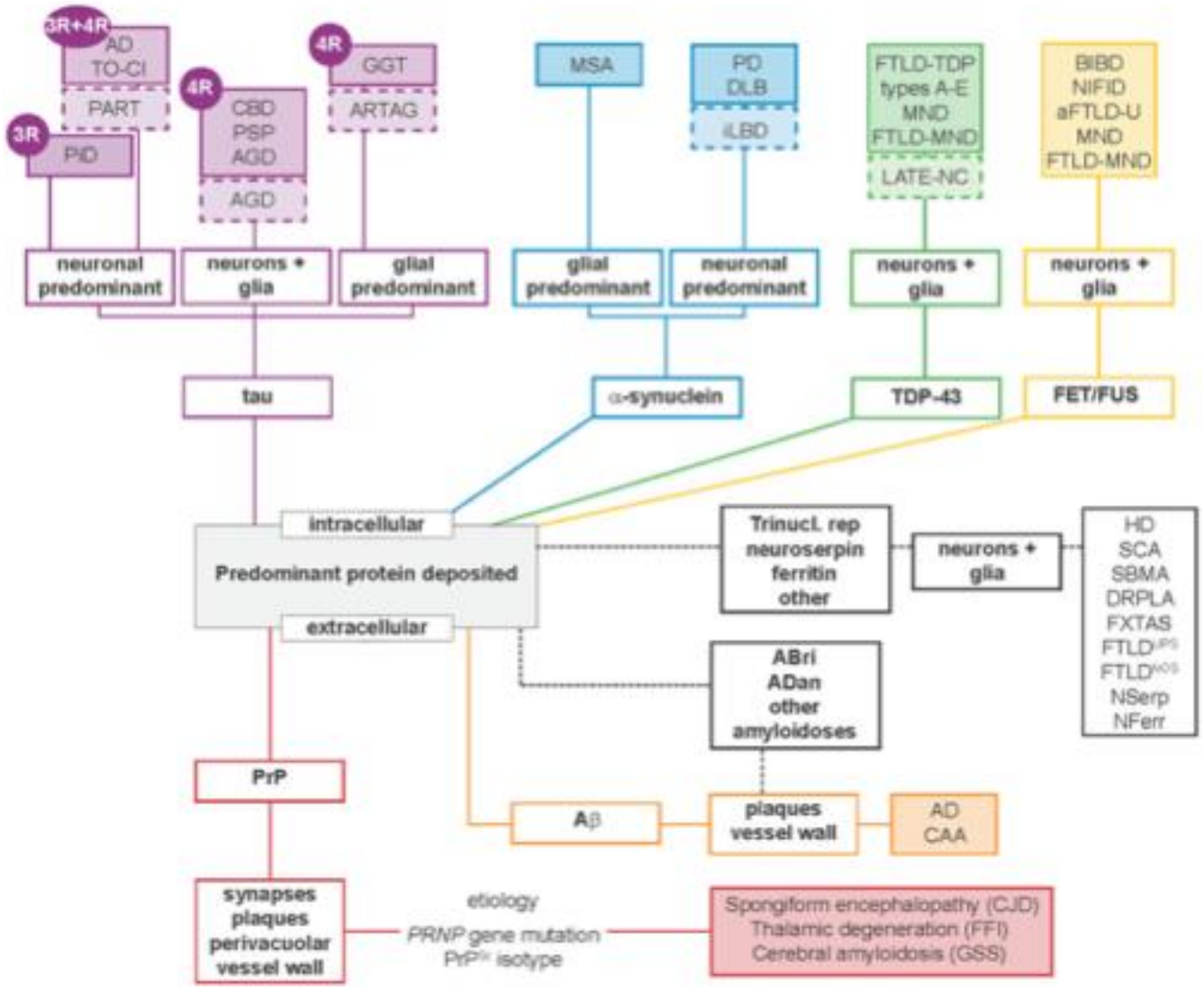
The Canadian Journal of Neurological Sciences (2022), 1–17
doi:10.1017/cjn.2022.34

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

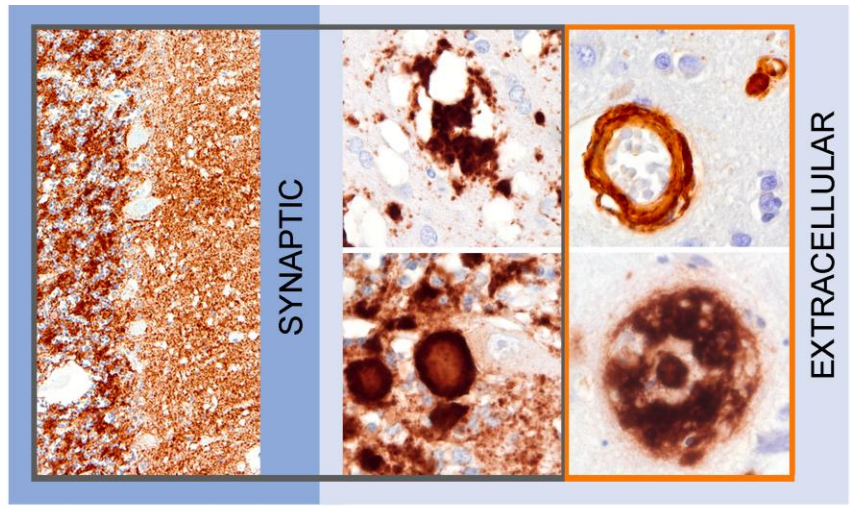
**Review Article**

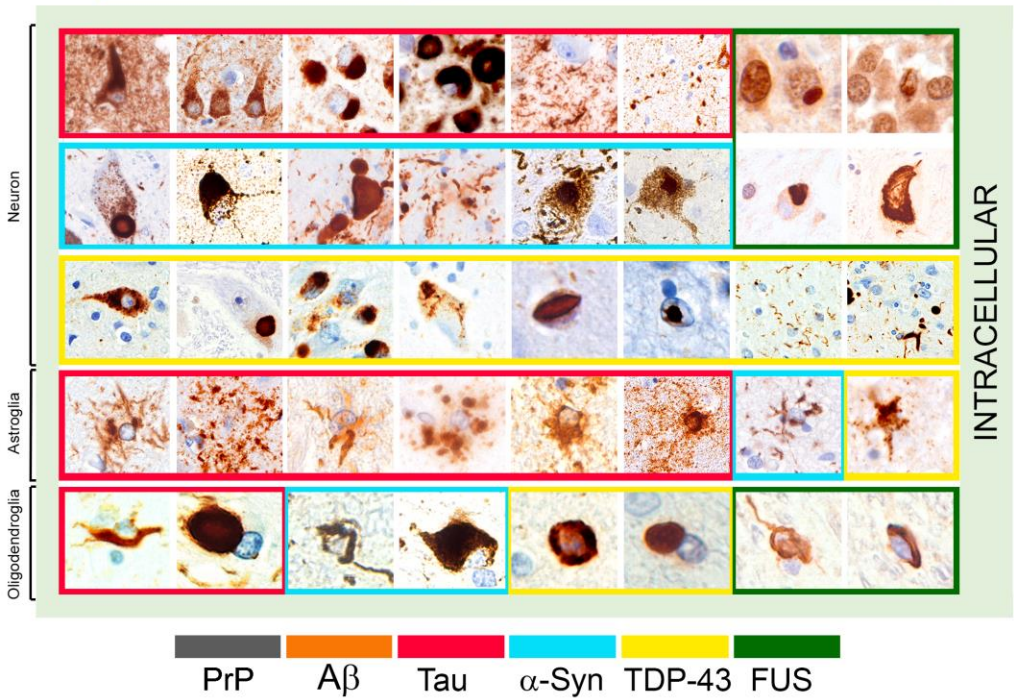
# Current Concepts of Mixed Pathologies in Neurodegenerative Diseases

Shelley L. Forrest[1] and Gabor G. Kovacs[2,3,4]




Kovacs GG, Ferrer I. Introduction Greenfield's Neuropathology 2024



*multiple neurodegenerative proteinopathies*

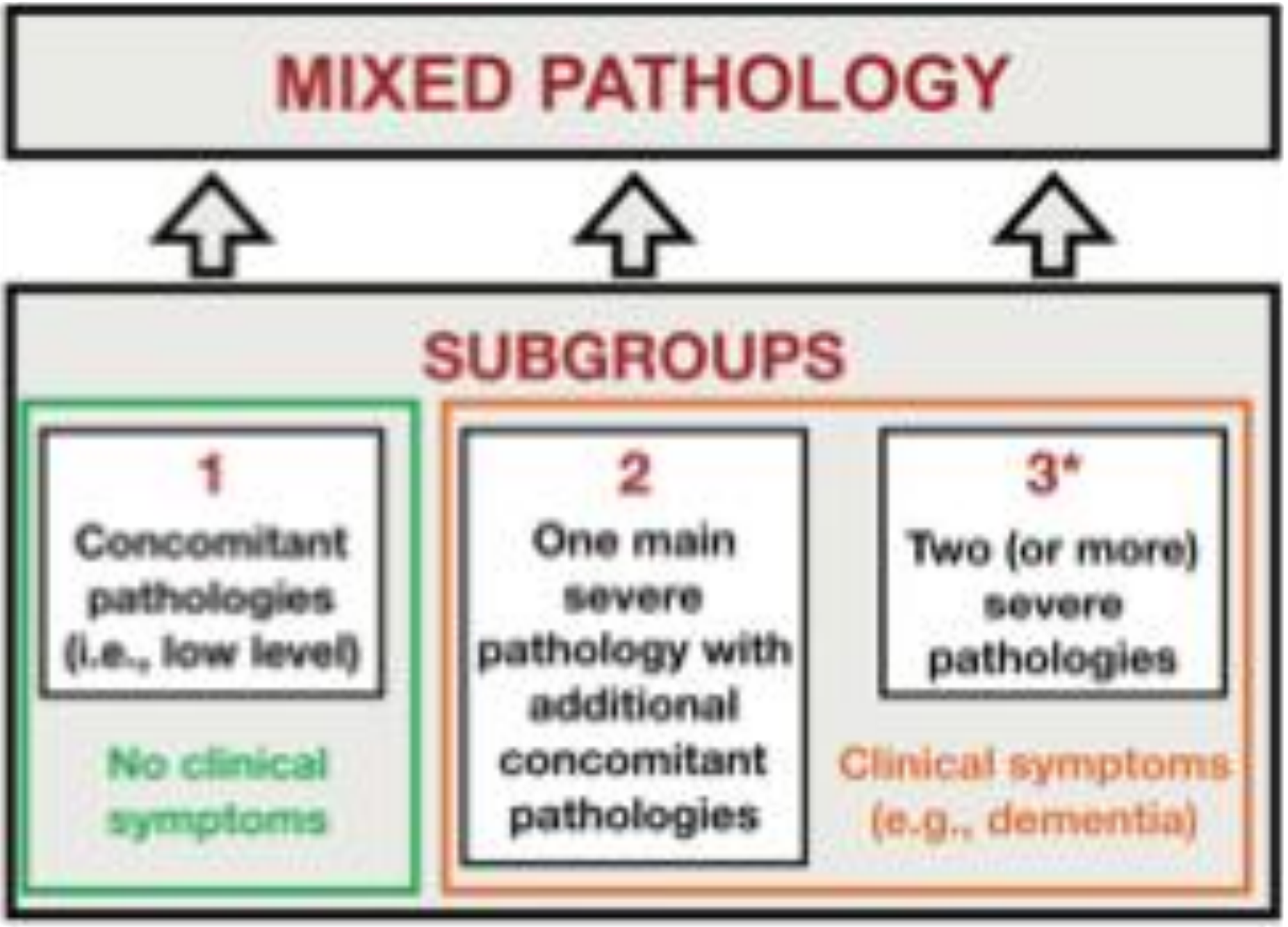
or

*neurodegenerative pathologies and another type of pathology* (e.g.,cerebrovascular disease)

**‘mixed pathology’**

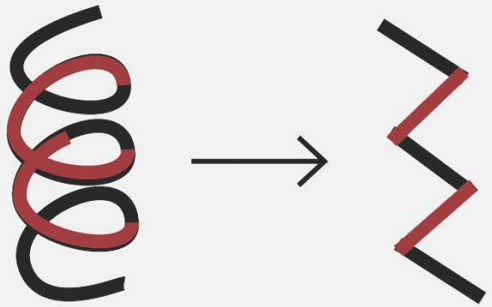
# Mixed pathologies of the ageing and neurodegenerating brain

Lauren Walker and Johannes Attems



conceptual level

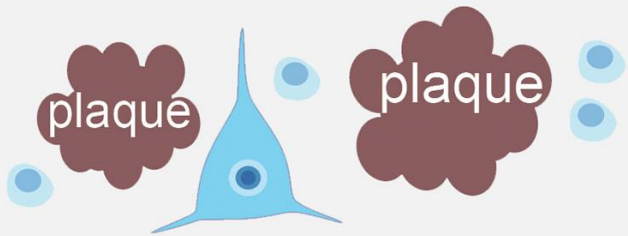
1 misfolded protein

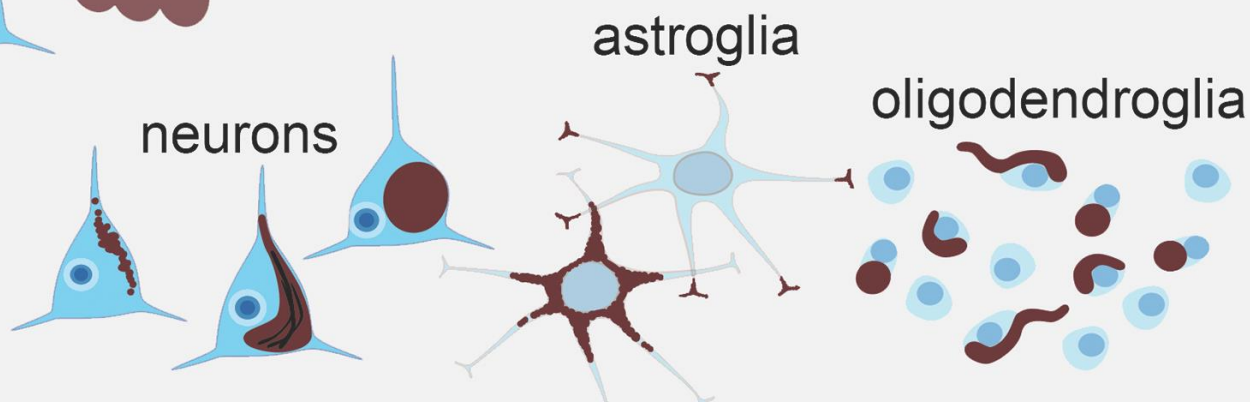


2 deposition pattern in disease-specific anatomical regions

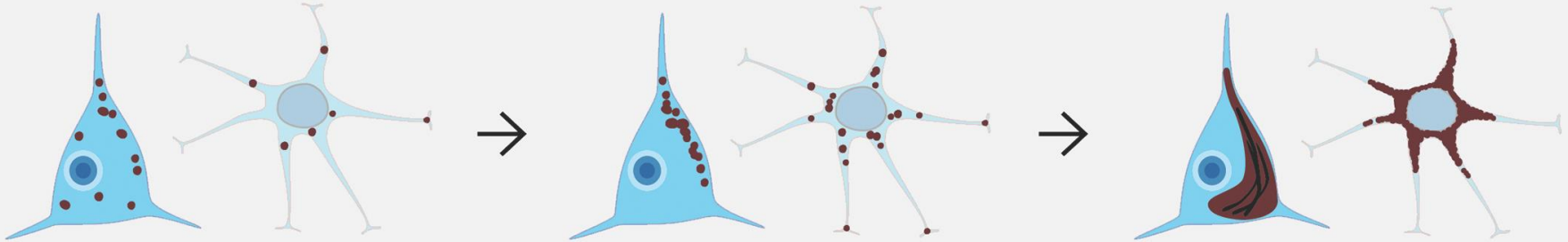
→ extracellular

→ intracellular
- neurons
- astrocytes
- oligodendroglia



## 3 maturation of protein deposits



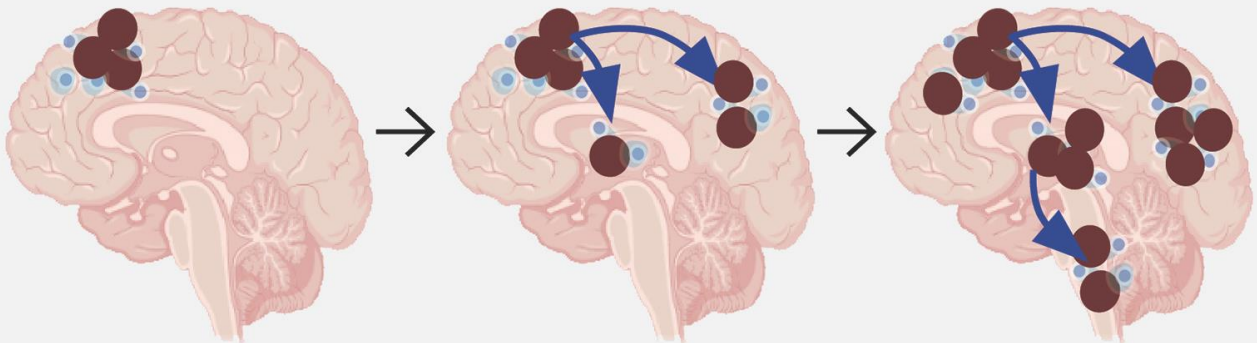
early biochemical changes → aggregation → fibrillization

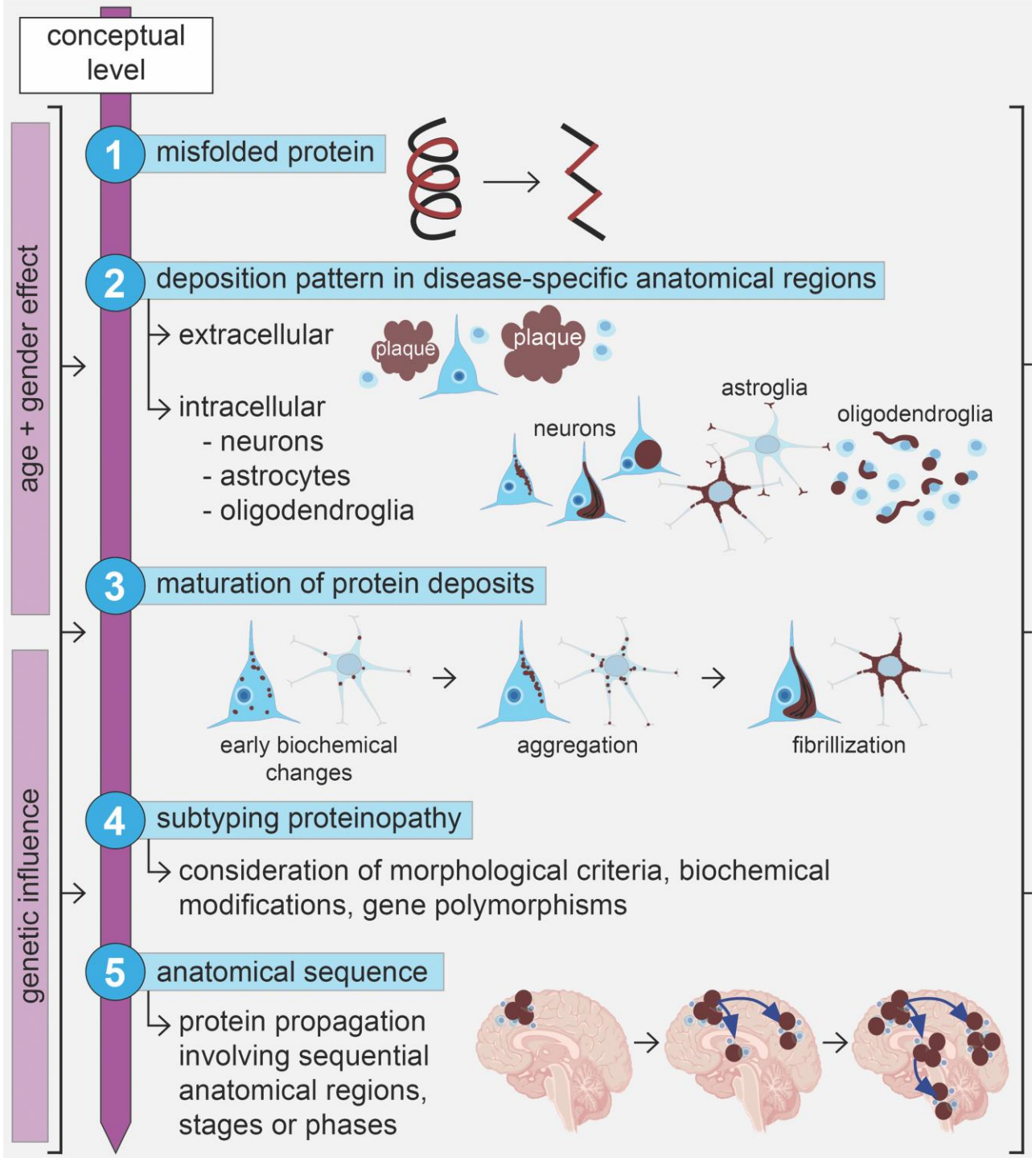
## 4 subtyping proteinopathy

→ consideration of morphological criteria, biochemical modifications, gene polymorphisms

## 5 anatomical sequence

→ protein propagation involving sequential anatomical regions, stages or phases




conceptual level
age + gender effect
genetic influence
1 misfolded protein
2 deposition pattern in disease-specific anatomical regions
extracellular
plaque
plaque
intracellular
- neurons
- astrocytes
- oligodendroglia
neurons
astroglia
oligodendroglia
3 maturation of protein deposits
early biochemical changes
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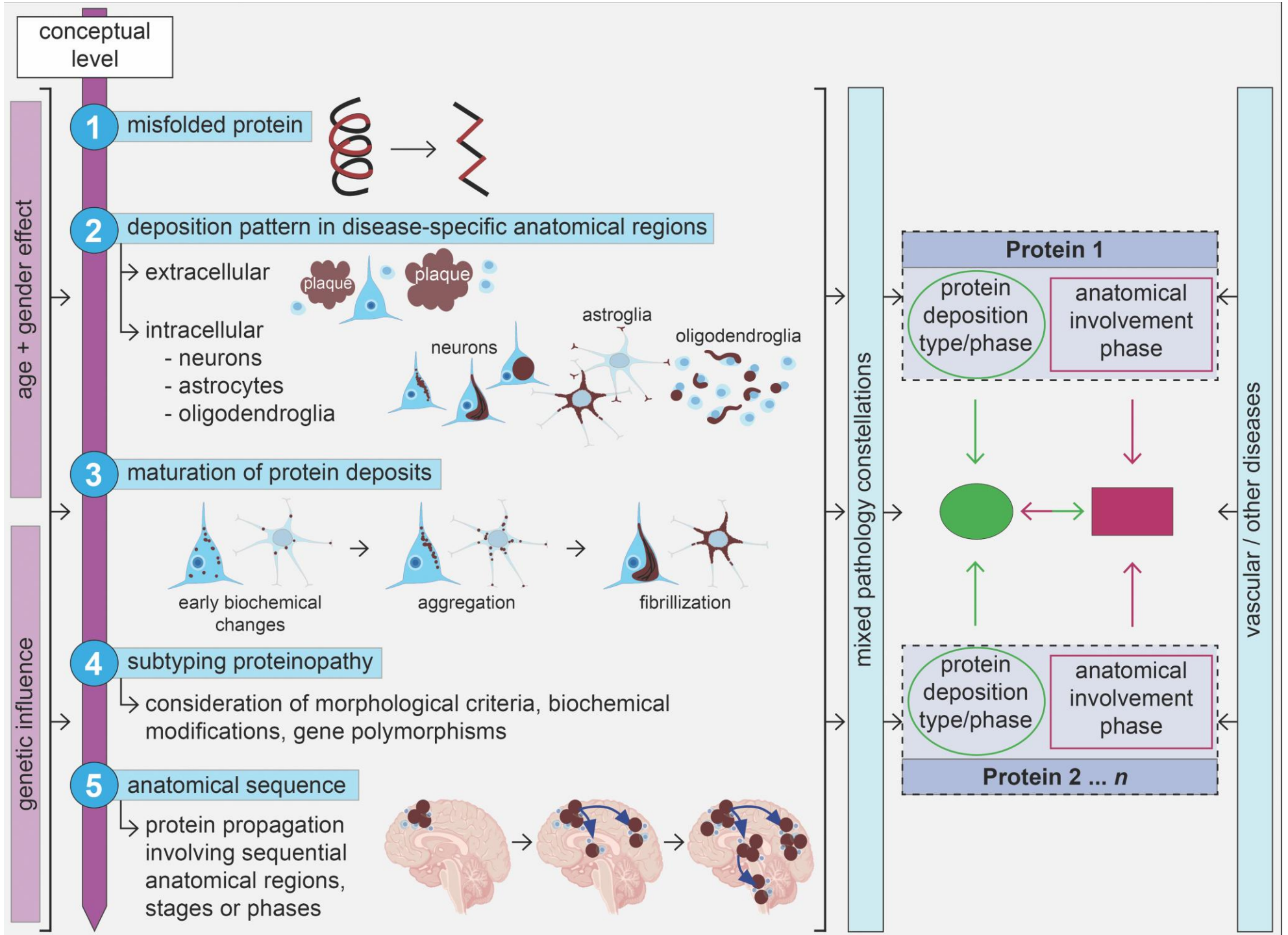
consideration of morphological criteria, biochemical modifications, gene polymorphisms
5 anatomical sequence
protein propagation involving sequential anatomical regions, stages or phases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4 subtyping proteinopathy
consideration of morphological criteria, biochemical modifications, gene polymorphisms
5 anatomical sequence
protein propagation involving sequential anatomical regions, stages or phases
mixed pathology constellations
Protein 1
protein deposition type/phase
anatomical involvement phase
protein deposition type/phase
anatomical involvement phase
Protein 2 ... n
vascular / other diseases

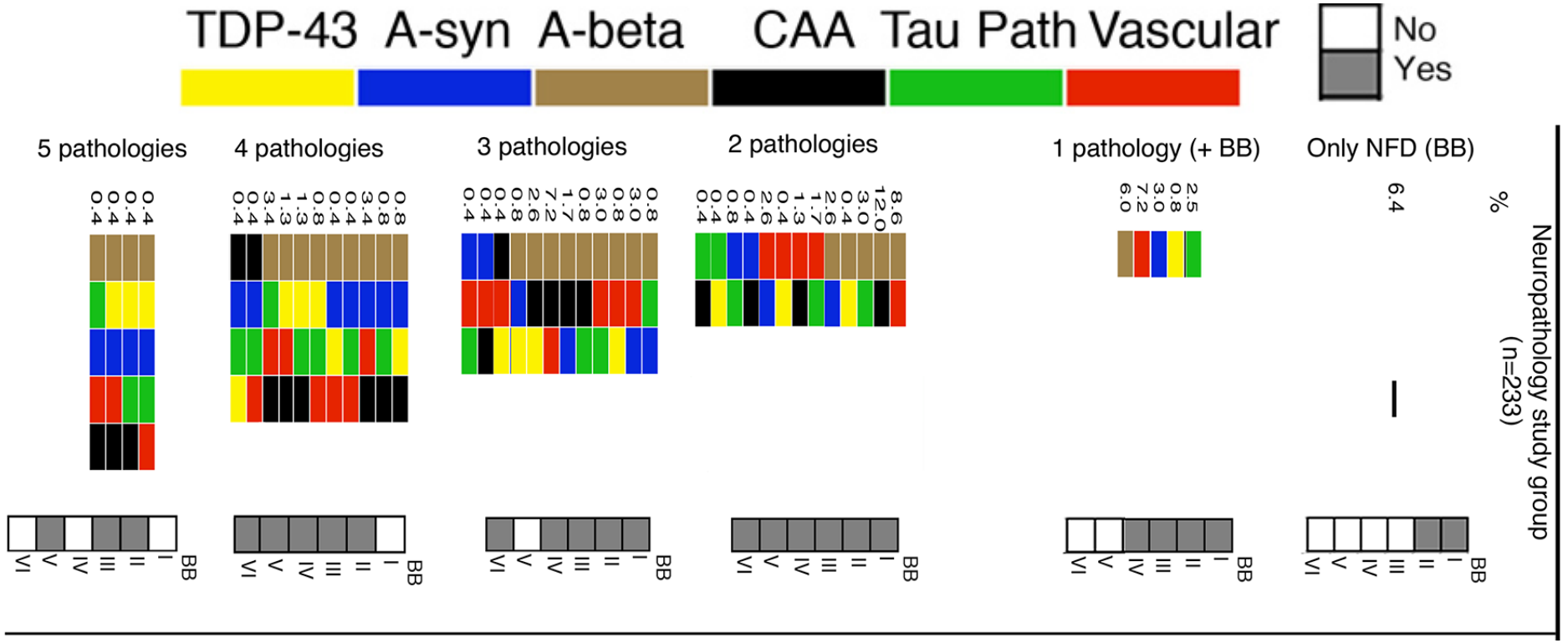
Acta Neuropathol (2013) 126:365–384
DOI 10.1007/s00401-013-1157-y

ORIGINAL PAPER

**Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series**

Gabor G. Kovacs · Ivan Milenkovic · Adelheid Wöhrer · Romana Höftberger · Ellen Gelpi · Christine Haberler · Selma Hönigschnabl · Angelika Reiner-Concin · Harald Heinzl · Susanne Jungwirth · Wolfgang Krampla · Peter Fischer · Herbert Budka

# The possible number of combinations is very high




- The **more advanced the Alzheimer`s disease pathology is, the more chance that there are further neurodegenerative pathologies** in the brain

# These studies used immunostainings also…

**Table 1 Overview of the community-based studies discussed in the present review**

| Study | Country |
|---|---|
| Rush Memory and Aging Project | USA |
| Religious Orders Study | USA |
| Medical Research Council Cognitive Function and Ageing Study | UK |
| Cambridge City Over-75 s Cohort | UK |
| Vantaa 85+ | Finland |
| Hisayama | Japan |
| Honolulu–Asia Aging Study | USA |
| Adult Changes in Thought | USA |
| Baltimore Longitudinal Study of Ageing | USA |
| Oregon Brain Aging Study | USA |
| 90+ Study | USA |
| Vienna Trans-Danube Aging study | Austria |

# OVERLAPPING PROTEINOPATHIES: BRIEF OVERVIEW OF THE LITERATURE

- Studies use different methodologies

**Table 2 Summary of methodological approaches used in the community-based neuropathological studies summarized in this review**

| Study | *n* | Neuropathological criteria | | | | | Aβ | Tau | α-Syn | Ubi/p62 | TDP-43 | Vascular pathologies | HS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BB | C | NR | NA | DLB/Br | | | | | | | |
| MAP [27,30-33] | 425 | + | + | + | | +[a] | + | + | + | | | + | + |
| ROS [27,30,32-35] | 539 | + | + | + | | +[a] | + | + | + | | +[b] | + | + |
| MRC CFAS [21,36-39] | 525 | + | + | | | +[a,c] | + | + | + | + | | + | + |
| CC75C + [40] | 224 | + | + | | | +[a] | + | + | + | + | | + | + |
| Vantaa 85 +[d] [41-43] | 304 | + | + | | | +[a] | + | + | + | + | | + | + |
| Hisayama [44,45] | 205 | + | | + | | +[e] | | + | + | + | | + | |
| HAAS [46-48] | 439 | + | + | | | +[e] | | | + | + | | + | + |
| ACT [49,50] | 438 | + | + | + | | +[e] | | | + | | | + | + |
| BALS [51,52] | 209 | + | + | | | +[e] | | | + | | | + | |
| OBAS[d] [53,54] | 125 | + | + | + | | +[e] | | + | + | | | + | + |
| 90+ Study[d] [55] | 108 | + | + | | | +[e] | + | + | + | | + | + | + |
| VITA [5] | 233 | + | + | + | + | +[c] | + | + | + | + | + | + | + |

Aβ, amyloid beta; ACT, Adult Changes in Thought; α-Syn, α-synuclein; BALS, Baltimore Longitudinal Study of Ageing; BB, Braak and Braak staging for Alzheimer's disease; Br, Braak; C, Consortium to Establish a Registry for AD criteria; CC75C, Cambridge City Over-75 s Cohort; DLB, McKeith criteria for dementia with Lewy bodies; HAAS, Honolulu–Asia Aging Study; HS, hippocampal sclerosis; MAP, Rush Memory and Aging Project; MRC CFAS, Medical Research Council Cognitive Function and Ageing Study; *n*, number of individuals included in the studies; NA, National Institute on Aging–Alzheimer's Association criteria; NR, National Institute on Aging–Reagan criteria; OBAS, Oregon Brain Aging Study; ROS, Religious Orders Study; TDP-43,Tar-DNA binding protein 43; Ubi, ubiquitin; VITA, Vienna Trans-Danube Aging study. [a]DLB criteria 1996. [b]Not assessed in all participants. [c]Braak staging for Parkinson's disease. [d]Age of autopsied cohort >90 years. [e]DLB criteria 2005.

alzheimer's research&therapy

REVIEW

# Prevalence of mixed pathologies in the aging brain

Jasmin Rahimi and Gabor G Kovacs*

**Table 3 Frequency of different neuropathological variables in community-based studies**

| Study | Alzheimer's disease-related pathologies | | | α-Syn | TDP-43 | HS | Vascular pathologies | Mixed pathology |
|---|---|---|---|---|---|---|---|---|
| | Braak III to VI | CERAD | NIA | | | | | |
| MAP [27,30] | | | 59% (195) | 15% (195) | | 13% (100) | 46%[a] (195) | 23% (195) |
| ROS [27,30,35] | | | 61% (386) | 21% (386) | 46% (130) | 13% (100) | 49%[a] (386) | 28% (386) |
| MRC CFAS [21,37] | 52% (456) | 46% (456) | | 39% (29% amygdala) (208) | | | 70%[b] (456) | |
| CC75C [40] | 39%[c] (213) | 28% (213) | | 15% (213) | | | 56%[d] (213) | |
| Vantaa 85+ [41-43] | 70% (304) | 66% (180) | 41%[e] (180) | 36% (304) | | 5% (132) | 55%[a] (132) | 40% (132) |
| Hisayama[f] [44,45] | | | 62% (205) | 29% (205) | | | 31% (29) | 10%[g] (29) |
| HAAS [48] | | | 19%[h] (363) | 10%[f] (363) | | 9%[f] (363) | 28%[d] (363) | 39.5% (363) |
| ACT [49] | 62% (438) | 47% (438) | | 14% (438) | | | 35%[d] (438) | |
| BALS [51,52] | | | 56%[i] (209) | 6%[f] (34) | | | 44%[a] (179) | |
| OBAS [53] | 62% (71) | 44% (71) | | 20% (71) | | 7% (71) | 46%[d] (71) | |
| 90+ Study [55] | | | 67% (108) | 6%[j] (108) | 31% (108) | 29%[f] (66) | | 19%[k] (108) |
| VITA [5] | 38% (233) | 35% (233) | | 25% (17.2% amygdala) (233) | 13% (233) | 3% (233) | 49%[l] (233) | 74% (233) |

Journal Canadien des Sciences Neurologiques

Review Article

# Current Concepts of Mixed Pathologies in Neurodegenerative Diseases

Shelley L. Forrest[1] and Gabor G. Kovacs[2,3,4]

**Table 3:** Prevalence (%) of mixed pathologies in community-based, longitudinal ageing studies and major neurodegenerative diseases

| Cohort | Type of pathology | AD-related | Aβ | NFT only/PART | Tau | | TDP-43 | α-synuclein | HS | CVD | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ARTAG | AGD | LATE-NC/other | LB pathology | | | |
| Community-based, longitudinal | ± cognitive impairment | 19–68 | ≤100 | ≤100 | 38 | 13 | 13–75 | 6–39 | 5–29 | 31–70 | 16,52,62,75 |
| Major proteinopathies reported in various studies | AD | 100 | 100 | – | 63 | 23–58 | 8–74 | 42–55 | 3–15 | 86 | 42,76,104,126 |
| | FTLD-tau | | | | | | | | | | |
| | PiD | 15 | 20 | – | 77 | n/d | 0 | 7–13 | n/d | n/d | 42,96 |
| | CBD | 11 | 41 | – | 100 | 100 | 15–45 | 10–13 | n/d | n/d | 42,93,96,127,128 |
| | PSP | 26 | 57 | – | 99 | 18–80 | 6–16 | 6–22 | n/d | n/d | 42,96,129–131 |
| | GGT | 2 | n/d | – | n/d | n/d | 7 | 5 | 1 | n/d | 132 |
| | FTLD-TDP | 5 | 42 | 50 | n/d | 7 | n/d | 6–15 | n/d | n/d | 42,96,133 |
| | MND | 5 | 36 | 45 | 41 | 37 | n/d | 6–11 | n/d | n/d | 42,57,106,134 |
| | LBD[1] | 10–100[2] | 50–100[2] | 16–63 | 56[4] | 10–25 | 2–52 | n/d | n/d | 38 | 42,57,126,135 |
| | MSA | 8 | 38 | 40 | 43 | n/d | 4–7 | 10 | n/d | n/d | 42,136,137 |
| | CJD | 38–50 | n/d | 69 | 15 | 6–8 | rare | 9–23 | n/d | n/d | 138–141 |

# NOT ONLY FOR SPORADIC DISEASE...

CURRENT OPINION

**Are comorbidities compatible with a molecular pathological classification of neurodegenerative diseases?**

*Gabor G. Kovacs*

**Table 1.** Overview of combined proteinopathies associated with representative genetic disorders

| Gene | Major protein | Tau | | | | | | | | | α-Syn | | | TDP-43 | | Aβ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ARTAG | PART | AGD | PSP | CBD | GGT | Pick | NFTs/ other | Only biochemical | Lewy body | MSA/ GCI | Only biochemical | NCI/ NNI | Only biochemical | Plaques | Only biochemical |
| *APP* | Aβ | − | − | − | − | − | − | − | + | − | + | − | − | − | − | + | − |
| *PSEN1* | Aβ | − | − | − | − | − | − | + | + | − | + | − | − | + | − | + | − |
| *PSEN2* | Aβ | − | − | − | − | − | − | − | + | − | + | − | − | + | − | + | − |
| *PRNP* | Prion protein | + | + | + | + | − | − | − | + | − | + | − | − | − | − | + | − |
| *TARDBP* | TDP-43 | + | − | − | − | − | − | − | + | − | − | − | − | + | − | − | − |
| *GRN* | TDP-43 | + | + | − | − | − | − | − | + | − | + | − | − | + | − | + | − |
| *C9orf72* | TDP-43 /DPR | +[a] | + | − | − | +[a] | − | − | + | − | + | − | − | + | − | + | − |
| *MAPT* | Tau | + | + | + | + | + | + | + | + | − | − | − | − | + | − | − | − |
| *HTT* | Huntingtin | + | + | − | − | − | − | − | + | + | − | − | + | + | + | + | + |
| *LRRK2* | αSyn | − | + | − | + | − | − | − | + | − | + | + | − | + | − | + | − |
| *SNCA* | αSyn | − | + | − | − | − | − | − | + | − | + | + | − | + | − | − | − |

# PATHOGENESIS

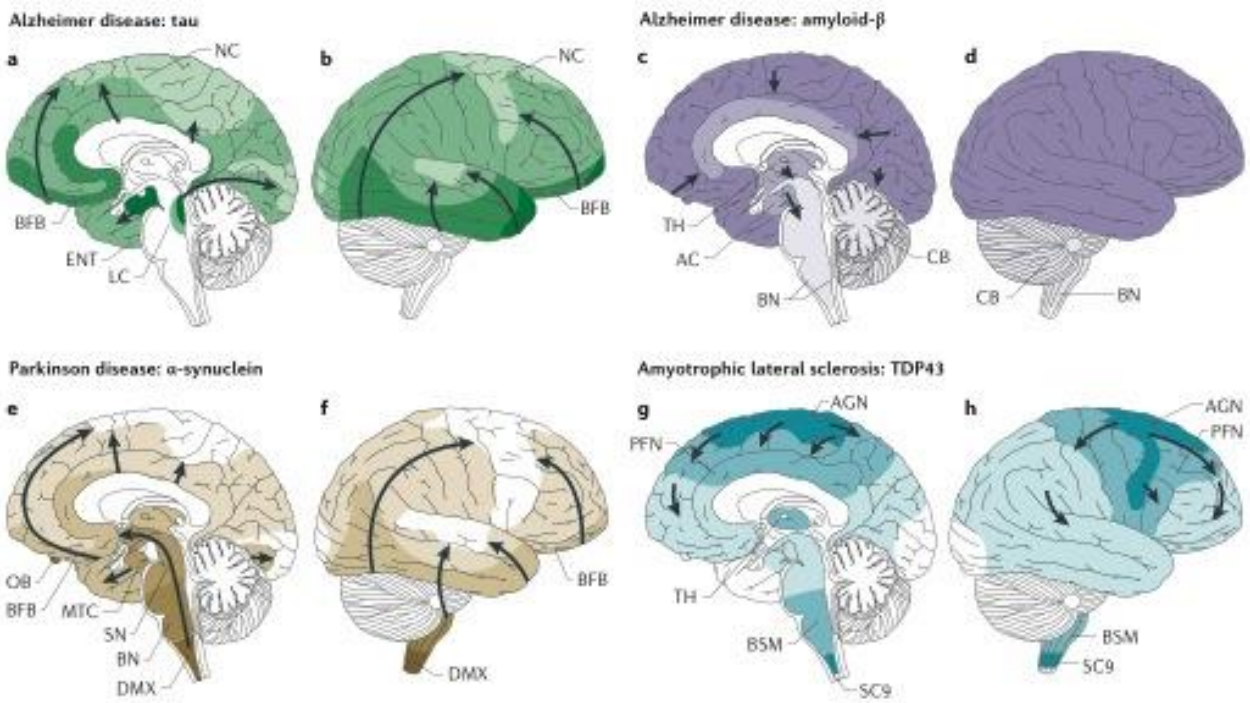
1. **Ageing as a risk factor**

2. **Direct and synergistic interactions** (i.e., cross-seeding) of proteins

3. A **pathogenic event is capable inducing aggregation of different proteins**, which suggests common pathways

4. As a provocative concept, **combined proteinopathies might represent distinct "strain-like" features**

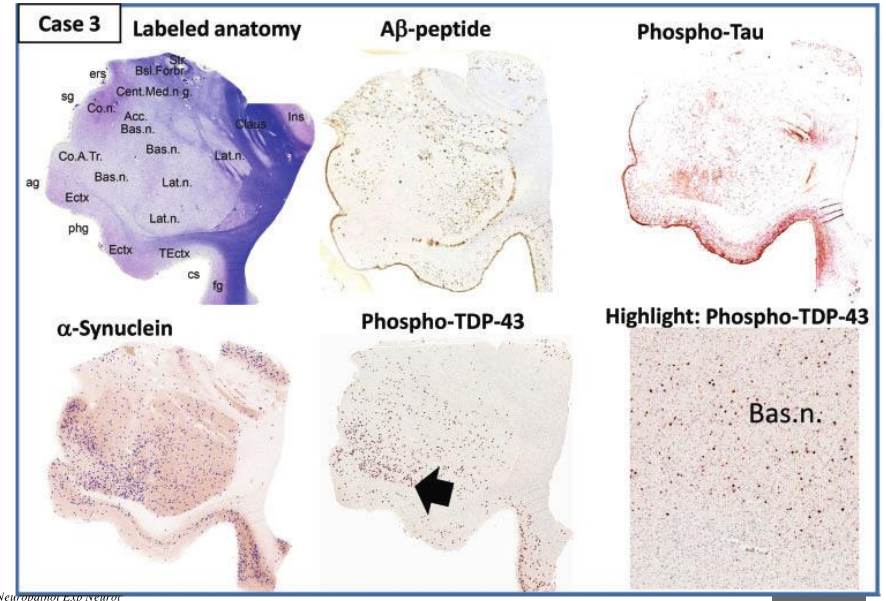
# For cross-seeding it is important that protein pathologies overlap (can meet!) in brain regions….






## AMYGDALA AS HOTSPOT

J Neuropathol Exp Neurol • Volume 77, Number 1, January 2018 Protein Misfolding in the Am




J Neuropathol Exp Neurol
Vol. 77, No. 1, January 2018, pp. 2–20
doi: 10.1093/jnen/nlx099
OXFORD

REVIEW ARTICLE

The Amygdala as a Locus of Pathologic Misfolding in Neurodegenerative Diseases

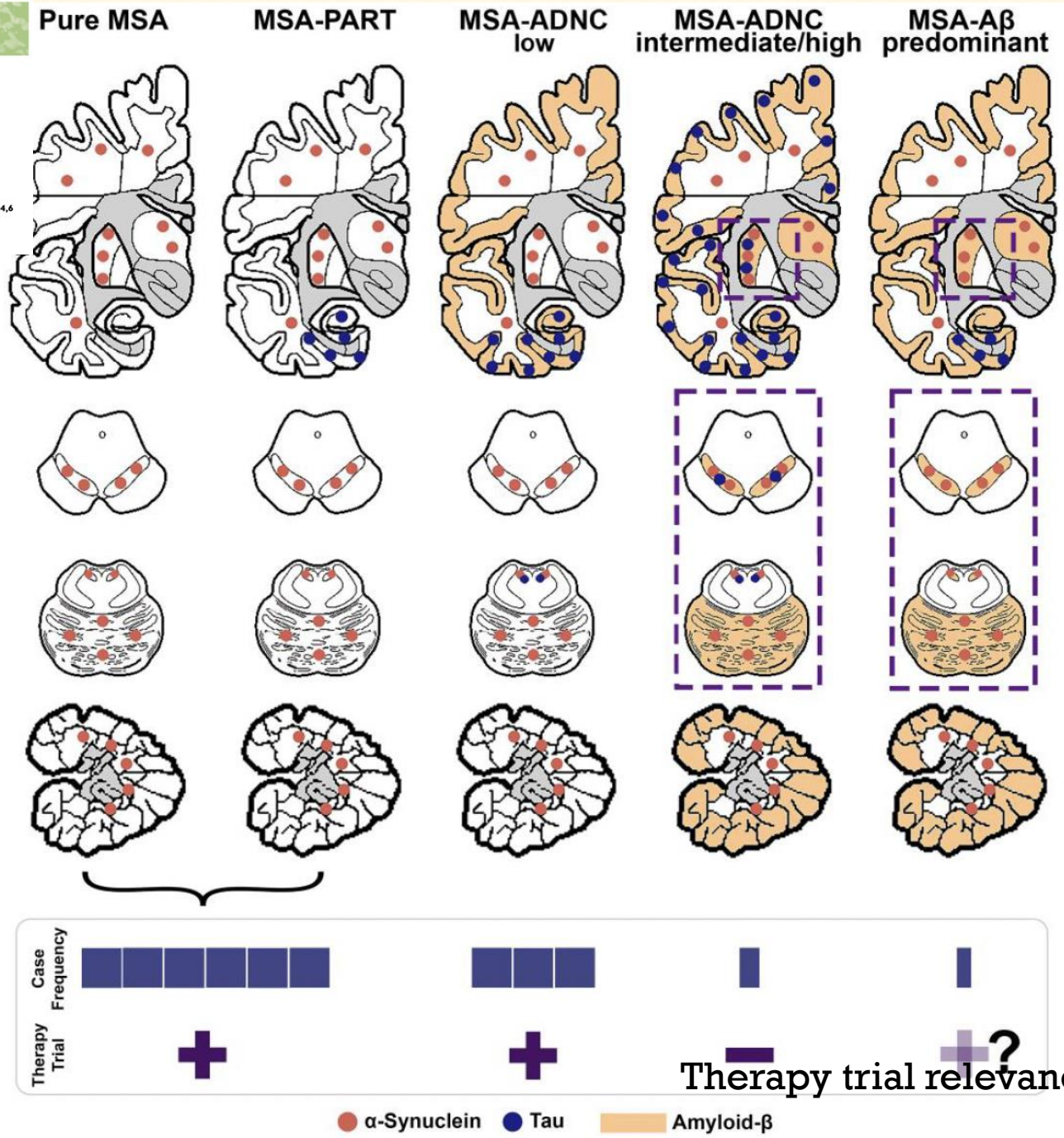
Peter T. Nelson, MD, PhD, Erin L. Abner, PhD, MPH, Ela Patel, Sonya Anderson, BA, Donna M. Wilcock, PhD, Richard J. Kryscio, PhD, Linda J. Van Eldik, PhD, Gregory A. Jicha, MD, PhD, Zsombor Gal, Ruth S. Nelson, Bela G. Nelson, Jozsef Gal, PhD, Md. Tofial Azam, MS, David W. Fardo, PhD, and Matthew D. Cykowski, MD

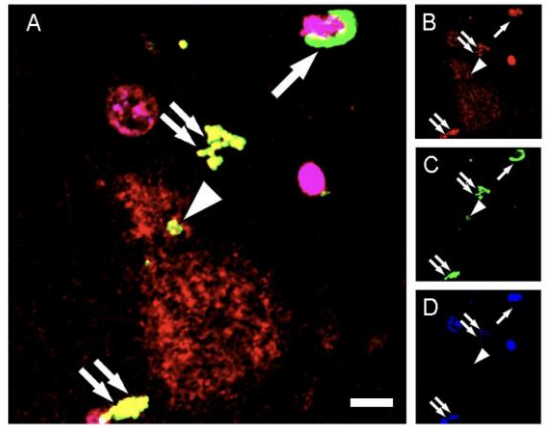
https://doi.org/10.1093/braincomms/fcae141 BRAIN COMMUNICATIONS 2024, fcae141 | 1

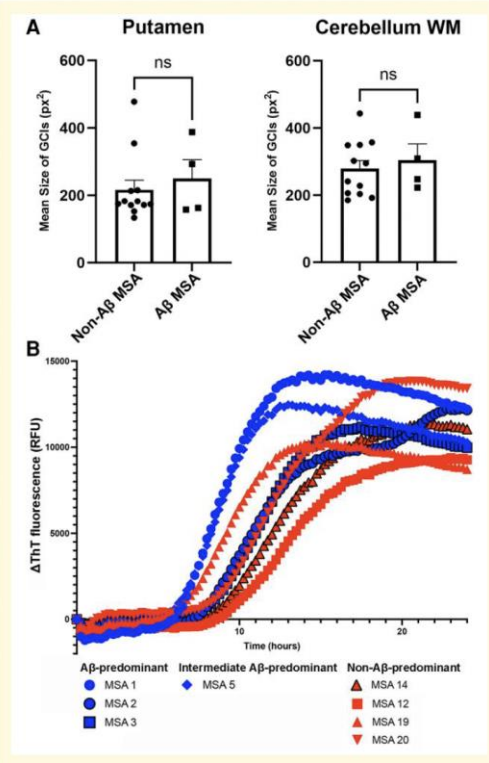
BRAIN COMMUNICATIONS

# Multiple system atrophy with amyloid-β-predominant Alzheimer's disease neuropathologic change

Tomoya Kon,[1,2] Shojiro Ichimata,[1,3] Daniel G. Di Luca,[4,5] Ivan Martinez-Valbuena,[1] Ain Kim,[1] Koji Yoshida,[1,3] Abdullah A. Alruwaita,[6,7] Galit Kleiner,[4,8] Antonio P. Strafella,[4,6] Shelley L. Forrest,[1,9,10] Christine Sato,[1] Ekaterina Rogaeva,[1] Susan H. Fox,[6] Anthony E. Lang[1,4,6] and Gabor G. Kovacs[1,4,6,9,10,11]




Therapy trial relevance

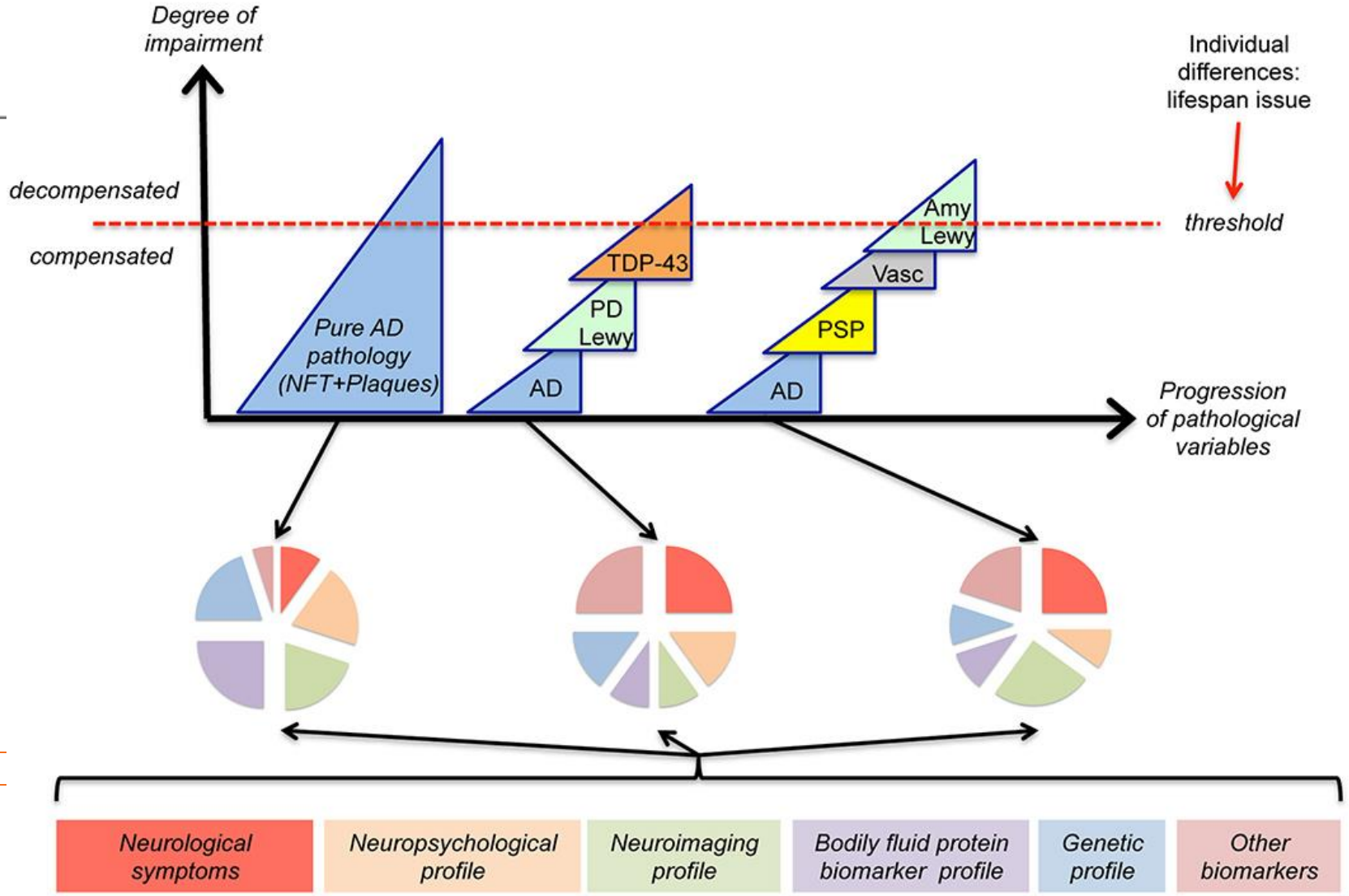
# BIOMARKER relevance

Acta Neuropathol (2010) 119:389–408
DOI 10.1007/s00401-010-0658-1

REVIEW

**Protein coding of neurodegenerative dementias: the neuropathological basis of biomarker diagnostics**

Gabor G. Kovacs · Gergő Botond · Herbert Budka




CURRENT OPINION

**Are comorbidities compatible with a molecular pathological classification of neurodegenerative diseases?**

*Gabor G. Kovacs*

# TAKE HOME MESSAGE

- Mixed pathology and Multimorbidity in individuals affected by neurodegenerative conditions is frequent (due to age) and includes systemic conditions with different pathogenesis than neurodegenerative diseases

- The most frequent additional proteinopathies are related to Alzheimer disease, Lewy body pathology, and limbic predominant TDP-43 proteinopathy

- The concept of comorbid proteinopathies has implications for biomarker and therapeutic development

- Ageing, synergistic interaction of proteins, common disease pathways and the influence of genetic variations are possible pathogenic players for comorbidity

- Concept of „lowering the threshold“ for dementia

- ***Dr. Bernardino Ghetti***

**Hereditary PrP Amyloidoses: Intersections and Overlaps**

- ***Dr. Rodrigo Morales***

**Cross-seeding of misfolded proteins: potential implications in disease**