Detection of abnormal prion protein in patients with non-prion disease dementia

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CREUTZFELDT-JAKOB DISEASE FOUNDATION, INC.

Supporting Families Affected by Prion Disease

CJD Foundation-supported studies: completed work and next steps

- PrP seeding activity studies have been completed in:
  - Alzheimer's disease (**AD**)
  - Frontotemporal dementia (**FTD**)

The Jeffrey and Mary Smith Family Foundation, contributed by Mary Smith, Zoë Smith Jaye, Jenny Smith Unruh

- Planned assessment of PrP seeding activity in additional neurodegenerative diseases:
  - corticobasal degeneration (**CBD**);
  - progressive supranuclear palsy (**PSP**);
  - Parkinson's disease (**PD**);
  - multiple system atrophy (**MSA**);
  - amyotrophic lateral sclerosis (**ALS**).

The Peggy J. Black Memorial Grant, contributed by Jim Black and Family
The Robert Vitanza Memorial Grant, contributed by Michael Vitanza
The Strides for CJD Grant, contributed by the Families of the CJD Foundation

Key problem

- To investigate whether misfolded PrP (PrP seeds) can be detected in the brain of patients diagnosed with Alzheimer's disease (AD) or frontotemporal dementia (FTD)

Why it is important

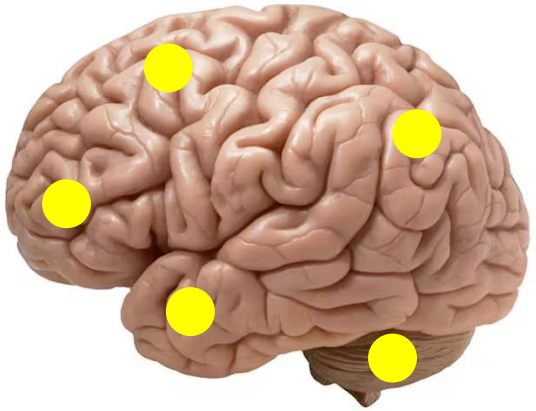
- If PrP seeds are present in AD/FTD, they may represent:
  - an early form of prion-related comorbidity;
  - a possible explanation for overlap between prion-like mechanisms and common dementias;
  - a new risk marker for patients with rapidly progressive dementia.

Main question of the study

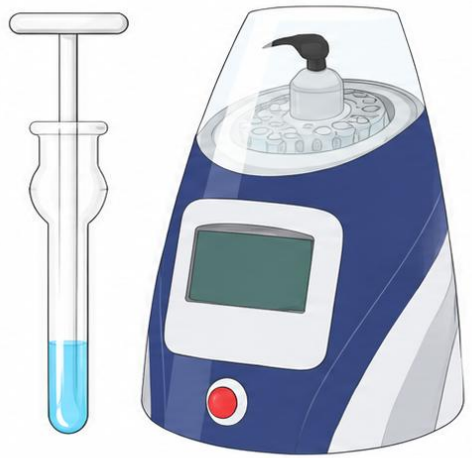
- Are some non-prion dementias associated with early PrP misfolding that resembles prion disease?

Experimental approach

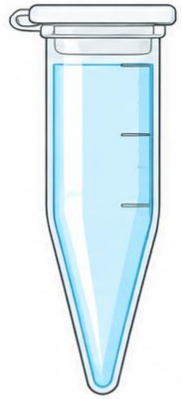
Preparation of human brain homogenates



Brain tissue sampling



Tissue homogenization



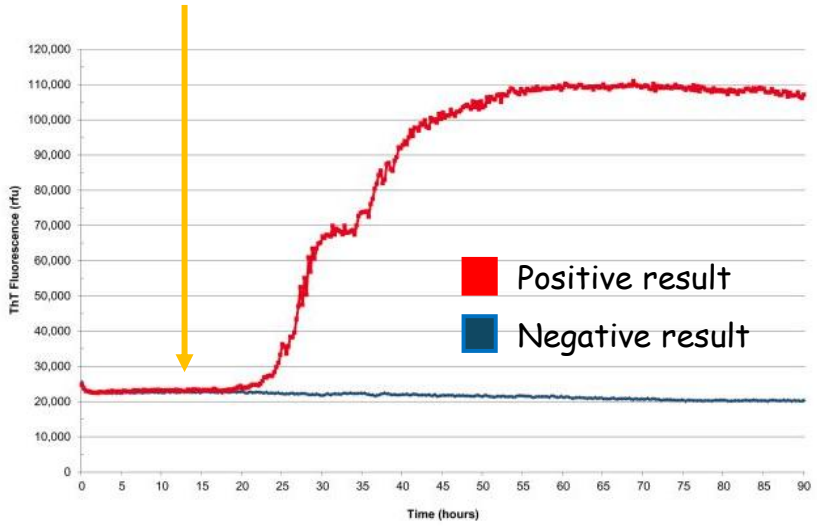
Final brain homogenate

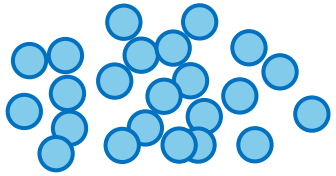
Experimental approach

Abnormal PrP was detected using Real-Time Quaking-Induced Conversion (RT-QuIC)

- Recombinant PrP substrate
- Brain homogenate ± PrP seed
- Thioflavin T fluorescence readout

Lag phase before exponential amplification

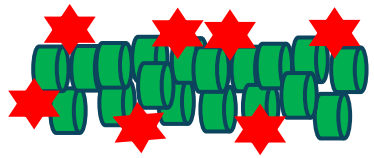




Substrate
(excess)

Seed
(diluted)

Seeded conversion

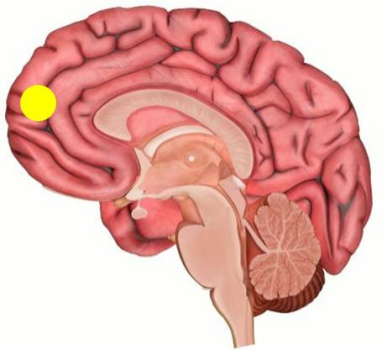


PrP amyloid fibrils

Experimental approach

Cases population	N cases	Age at death (years; mean±SD)
DEMENTED		
• Alzheimer's disease (AD)	101	80±10
• Frontotemporal dementia (FTD)	9	71±11
• Others	3	72±5
NON-DEMENTED (negative controls)		
• Young subjects	20	39±12
• Old subjects	45	79±10

Number of brain regions tested



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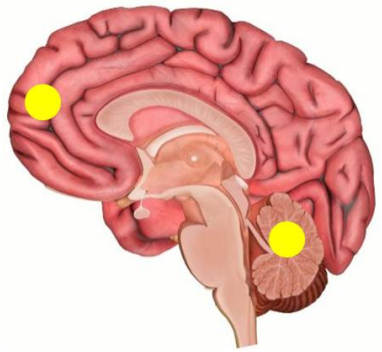

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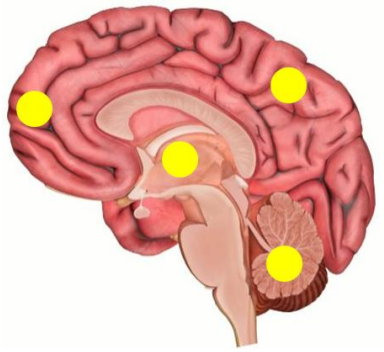

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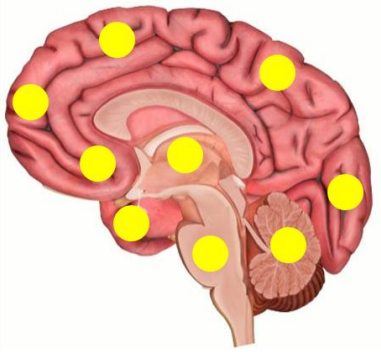

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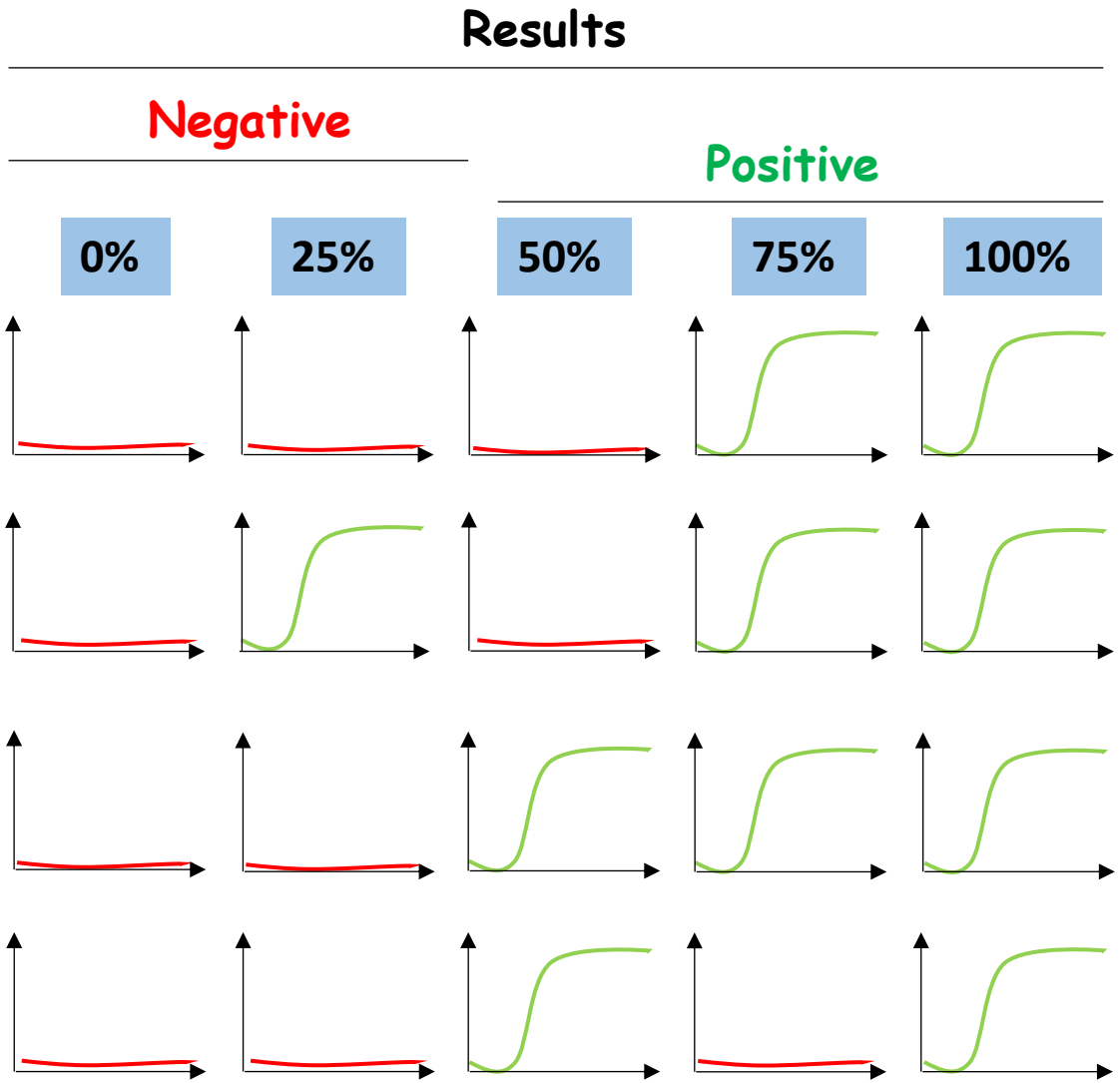
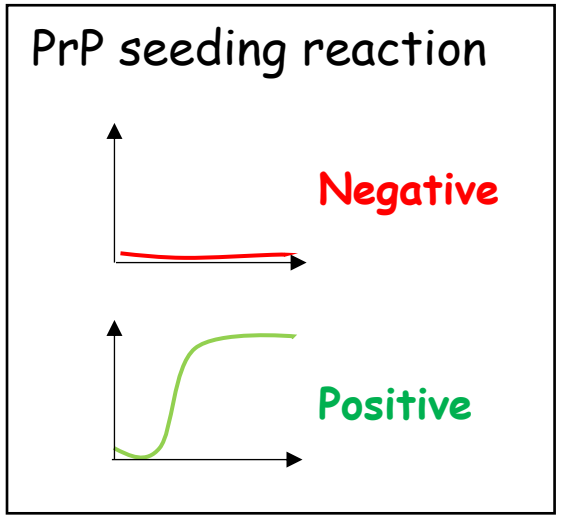
Experimental approach

Samples are classified as RT-QuIC positive when at least 2 out of 4 replicate wells show a positive signal





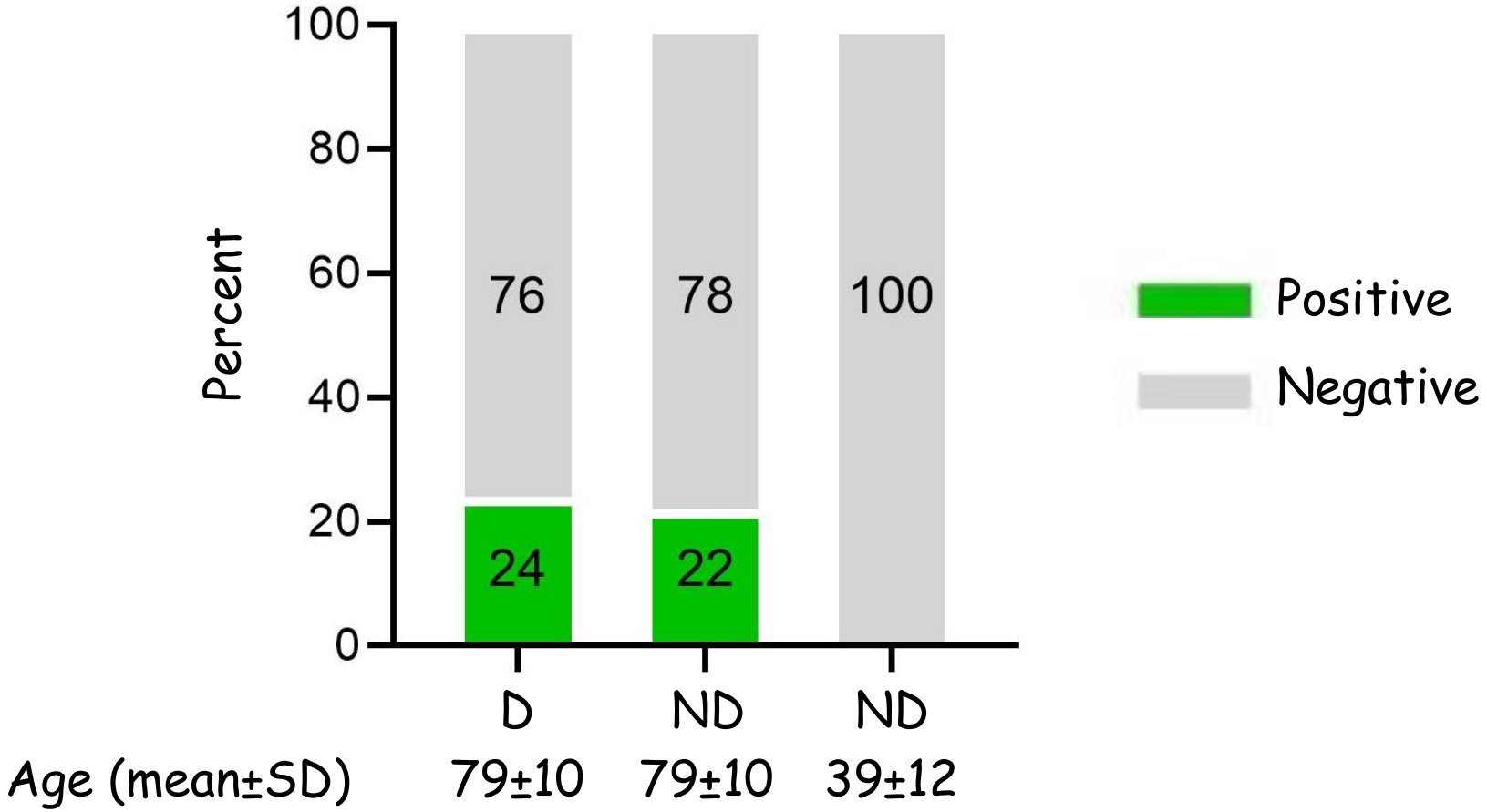
Experimental approach

N experiments (RT-QuIC)

	1	2	3	4	5	Results	Degree positive outcome
Sample 1						Negative	
Sample 2						Negative	
Sample 3						Positive	Low (1/5)
Sample 4						Positive	Moderate (2/5)
Sample 5						Positive	High (≥3/5)
Sample 6						Positive	High (≥3/5)

Results

PrP RT-QuIC positivity in *Demented* (D) and *non-demented* (ND) cases

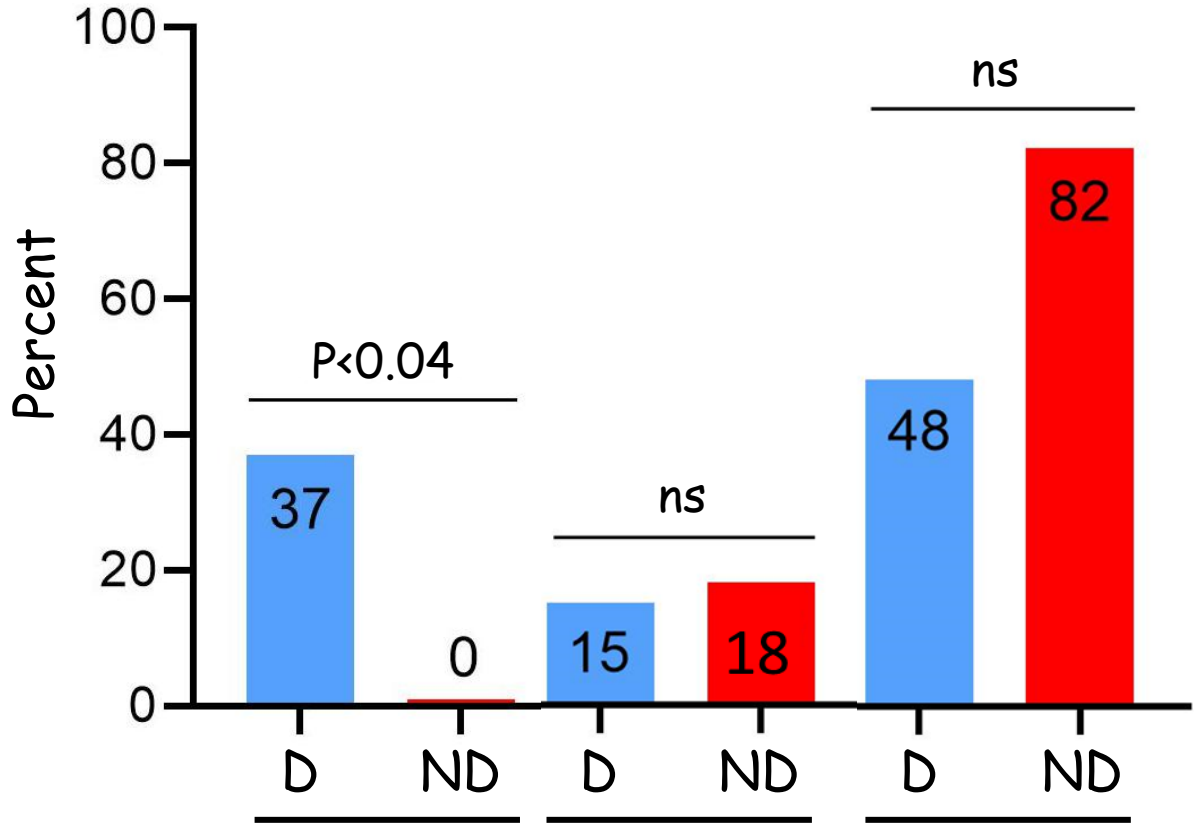


Conclusion: PrP RT-QuIC positivity is comparable in demented and age-matched non-demented cases, suggesting an age-associated rather than dementia-specific phenomenon.

Results

Degree positive outcome in cases with positive PrP RT-QuIC

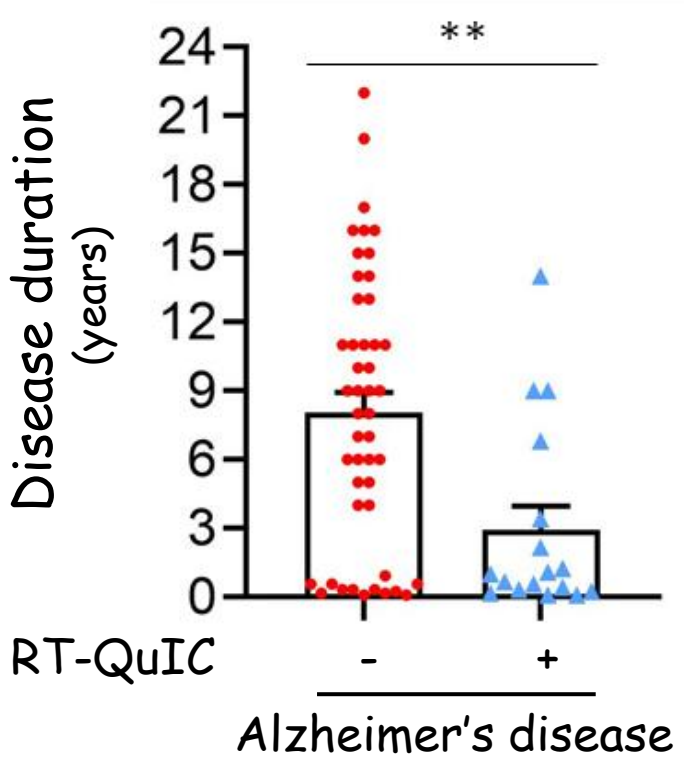
Degree positive outcome
Low (1/5)
Moderate (2/5)
High (≥3/5)



Conclusion: Only high PrP RT-QuIC positivity discriminates demented from non-demented cases.

Results

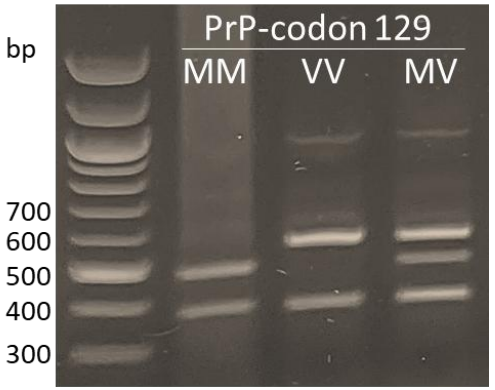
PrP RT-QuIC positivity is associated with shorter disease duration in Alzheimer's disease

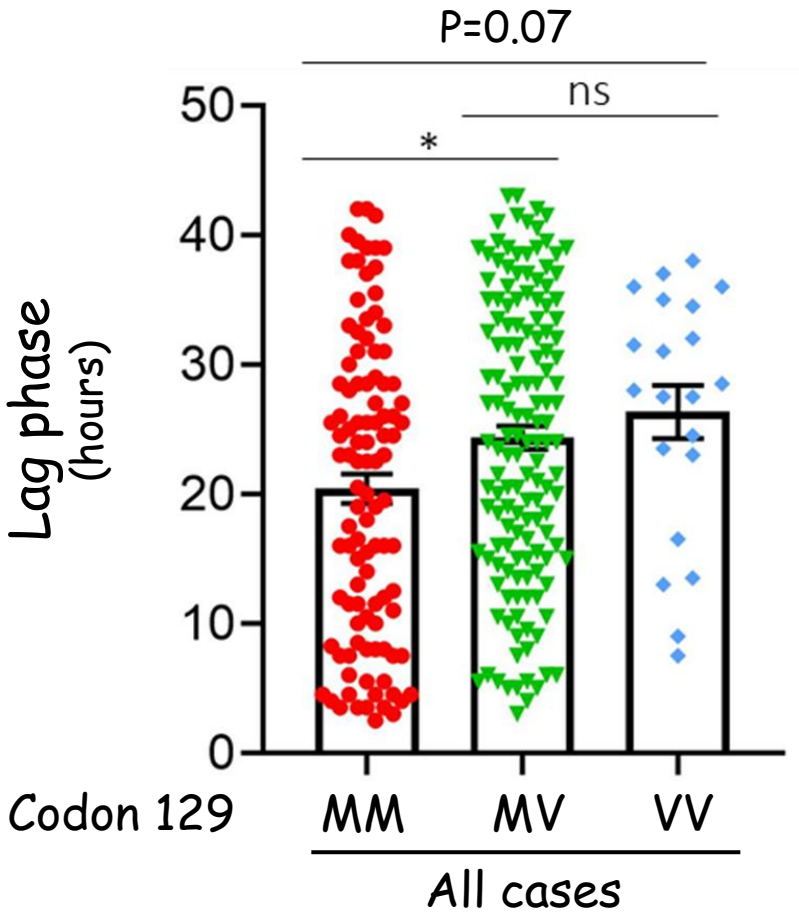


Conclusion: AD cases with positive PrP seeding showed shorter disease duration, suggesting an association with faster disease progression

Results

PrP codon 129 genotype modulates RT-QuIC lag phase

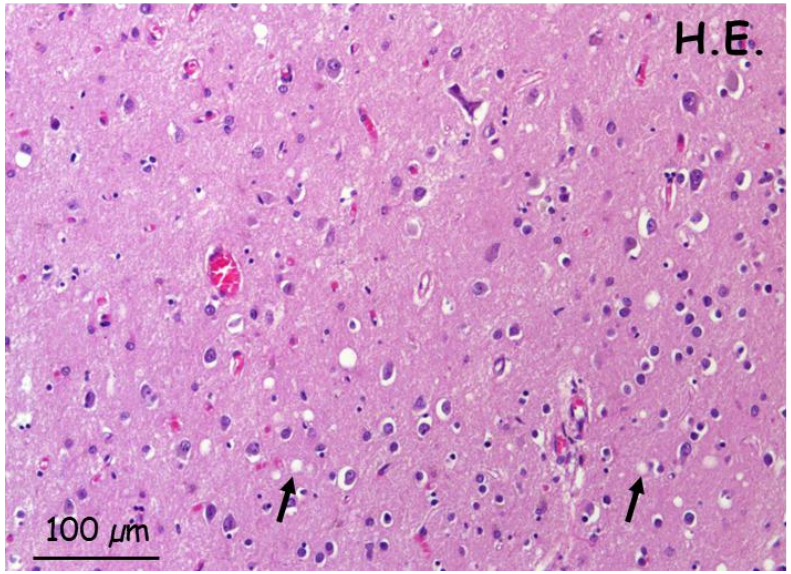




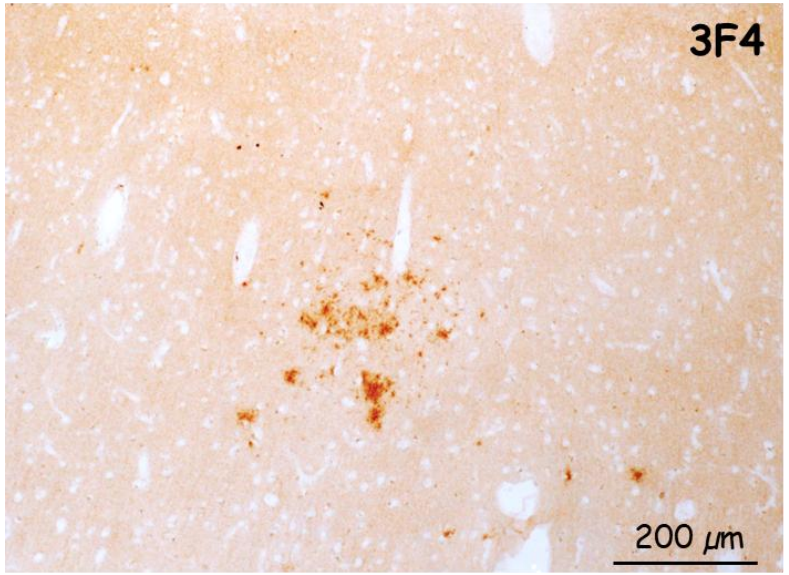
Conclusion: The 129MM genotype is associated with a shorter RT-QuIC lag phase, suggesting more efficient PrP seeding/conversion.

Results

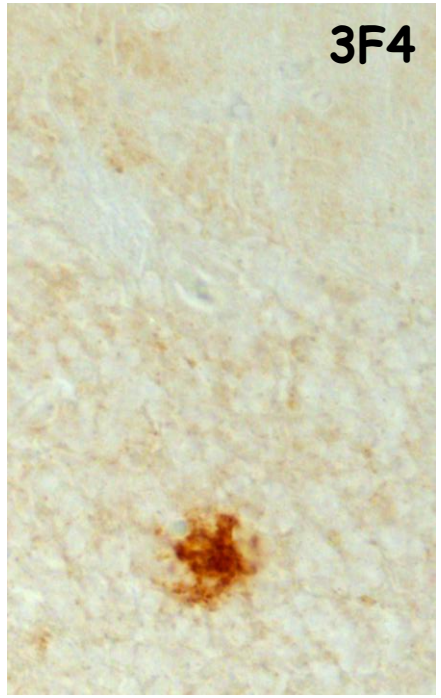
Histopathology of RT-QuIC positive cases



Frontal cortex



Temporal cortex



Cerebellum

Conclusion: Spongiform degeneration and/or PrP deposits may be found in cases with positive PrP seeding activity

Conclusions

- Our findings suggest that PrP misfolding may occur as a comorbid or secondary process in a subset of non-prion dementias. While low-level PrP seeding can also be detected in aged non-demented brains, strong PrP seeding activity may identify a biologically relevant subgroup of dementia cases with faster progression and prion-like molecular features;

- *PRNP* codon 129 modulated seeding efficiency, with 129MM showing shorter RT-QuIC lag phases;

- **Take home message**: In patients with AD and FTD, misfolded PrP may represent an early stage of prion-related comorbidity;

- A key remaining question is whether RT-QuIC–detectable abnormal PrP in AD and FTD has biological relevance beyond seeding activity, including potential transmissibility.

Summary slide

Misfolded PrP in AD and FTD may mark an early prion-related comorbidity.

Low-level PrP seeding can appear with aging, but strong RT-QuIC positivity identifies a subset of dementia cases with faster progression and prion-like molecular features.

Next step: test the same seeding-activity rationale across additional neurodegenerative diseases

Acknowledgments

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- Zoë Smith Jaye
- Jenny Smith Unruh

The National Prion Disease Pathology Surveillance Center

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- Zerui Wang lab
- Witold Surewicz lab

Cleveland Alzheimer's Disease Research Center

NIH National Institute on Aging

CDC Centers for Disease Control and Prevention

Thank you