

Prions for Neuropathology Fellows (and Friends)

Mark Cohen, MD
Professor of Pathology & Neurology
University Hospitals of Cleveland
Case Western Reserve University



AMERICAN ASSOCIATION
OF NEUROPATHOLOGISTS

Disclosures

- I have no relevant financial relationships to disclose
- **OR**
- I have the following relevant financial relationships to disclose

YOUR COMPANY NAME HERE



Learning Objectives

**I'M GLAD I LEARNED
ABOUT PARALLELOGRAMS IN
HIGH SCHOOL MATH INSTEAD
OF HOW TO DO MY TAXES.
IT COMES IN SO HANDY DURING
PARALLELOGRAM SEASON.**

1. Discuss the diagnostic value of cerebrospinal fluid biomarkers for prion diseases, including why most patients with cerebrospinal fluid 14-3-3 protein do not have prion disease.
2. Describe anatomic variability in the histopathological hallmarks of prion disease.
3. Find reliable information regarding proper handling of potentially prion positive biomaterials



Accomplishing our learning objectives

1. Helping the Doctors
2. Prions under glass
 1. Horses
 2. Zebras (or, plaques I have known)
 3. Unicorns (knowing our limitations)
3. When Prions escape



CLINICAL HISTORY: Other Comments; Concern for CJF (no history anoxic brain injury)

COMPARISON: MR brain November 09, 2021

TECHNIQUE:

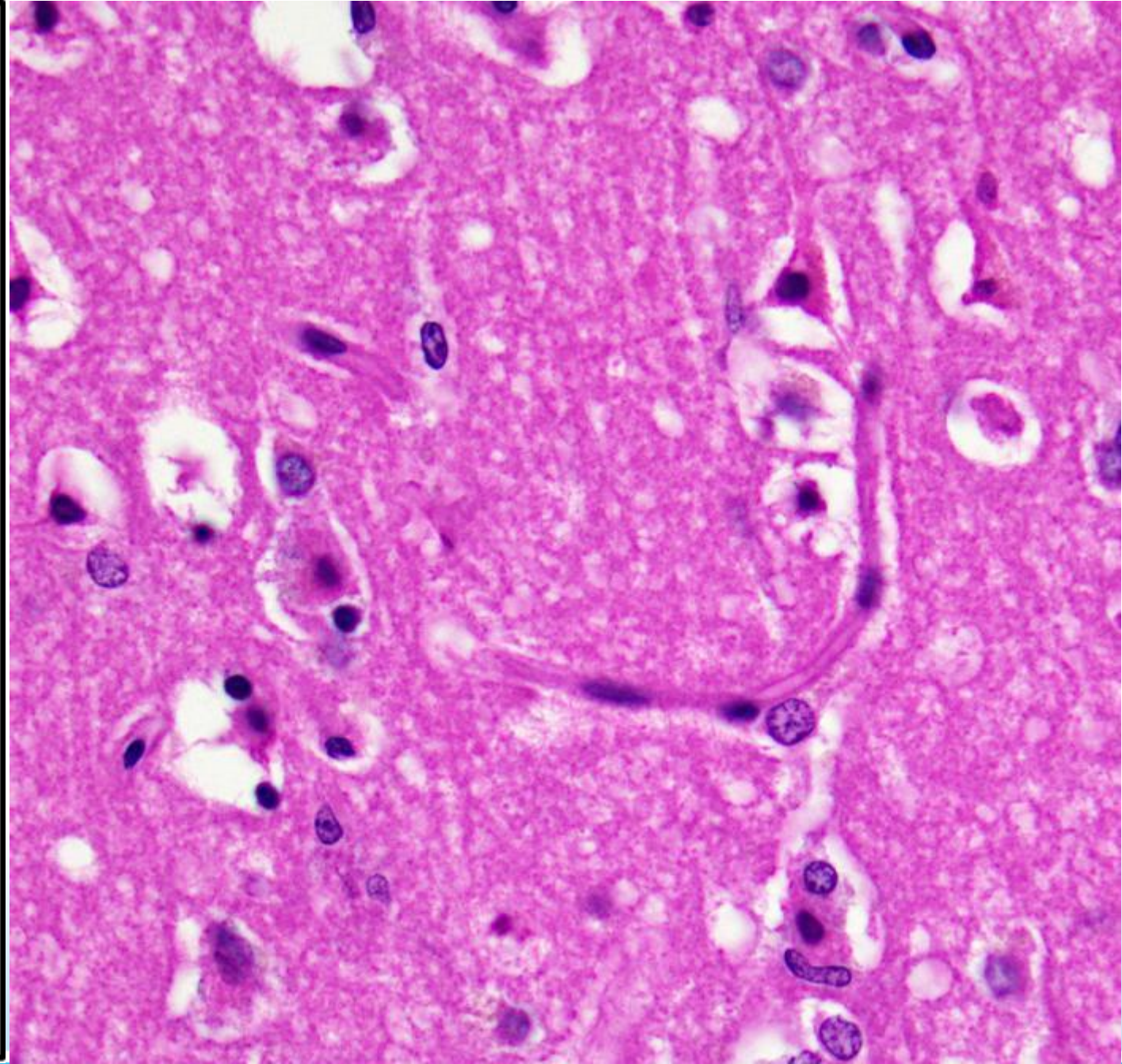
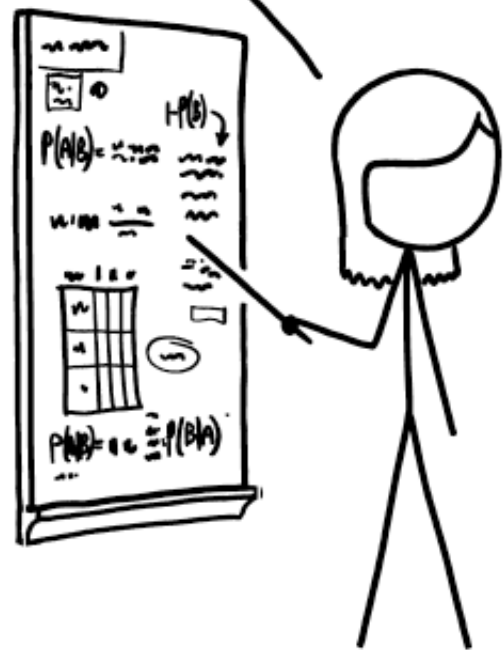
Sagittal T1 weighted, axial T2 weighted, axial diffusion weighted and axial T2-weighted FLAIR images of the brain were obtained.

IMPRESSION:

Supratentorial cortical and deep nuclei restricted diffusion with T2 FLAIR hyperintense signal suggestive of status epilepticus though differentials include but not limited to Creutzfeldt-Jakob disease, encephalitis or hypoglycemic encephalopathy.

GIVEN THESE PREVALENCES,
IS IT LIKELY THAT THE TEST
RESULT IS A FALSE POSITIVE?

WELL, THIS CHAPTER IS ON
BAYES' THEOREM, SO YES.






Helping the Doctors I: Our Man in Milan

JAMA Neurology | Original Investigation

Evaluation of a New Criterion for Detecting Prion Disease With Diffusion Magnetic Resonance Imaging

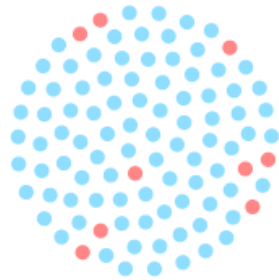
Alberto Bizzi, MD; Riccardo Pascuzzo, PhD; Janis Blevins, BSc; Marina Grisoli, MD; Raffaele Lodi, MD; Marco E. M. Moscatelli, MD; Gianmarco Castelli, MSc; Mark L. Cohen, MD; Lawrence B. Schonberger, MD; Aaron Foutz, MSc; Jiri G. Safar, MD; Brian S. Appleby, MD; Pierluigi Gambetti, MD

Subtype Diagnosis of Sporadic Creutzfeldt–Jakob Disease with Diffusion Magnetic Resonance Imaging

Alberto Bizzi, MD ¹, Riccardo Pascuzzo, PhD ¹, Janis Blevins, BSc,² Marco E. M. Moscatelli, MD ¹, Marina Grisoli, MD,¹ Raffaele Lodi, MD,^{3,4} Fabio M. Doniselli, MD,¹ Gianmarco Castelli, MSc,¹ Mark L. Cohen, MD,^{2,5,6} Aymeric Stamm, PhD,⁷ Lawrence B. Schonberger, MD,⁸ Brian S. Appleby, MD,^{2,5,6,9} and Pierluigi Gambetti, MD⁵

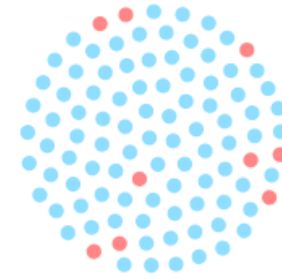


Helping the Doctors II: CSF testing for prion disease

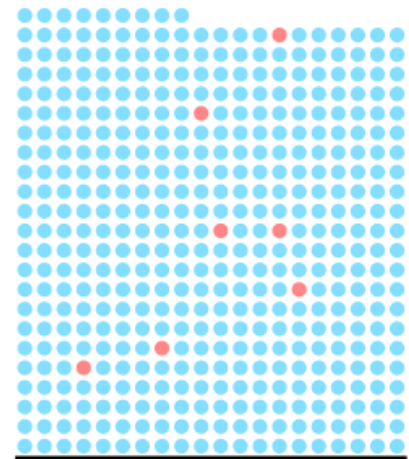
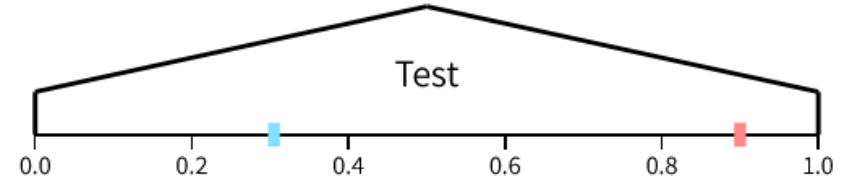
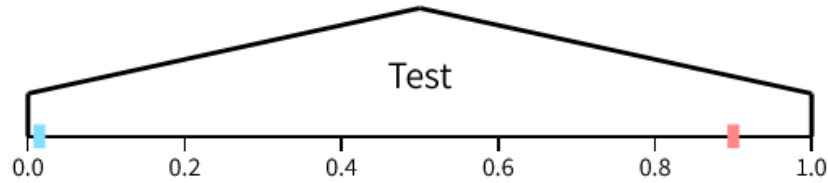


Population

Prior probability at NPDPSC has doubled over the last decade (good)

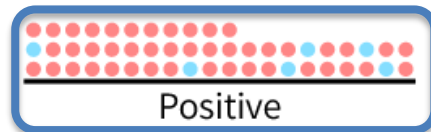


Population

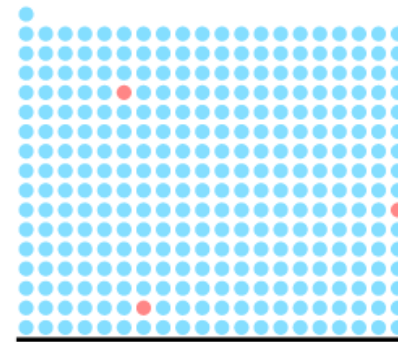


Negative

RT-QuIC is nearly/
may be 100% specific (good)

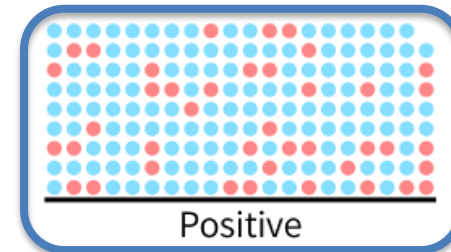


Positive

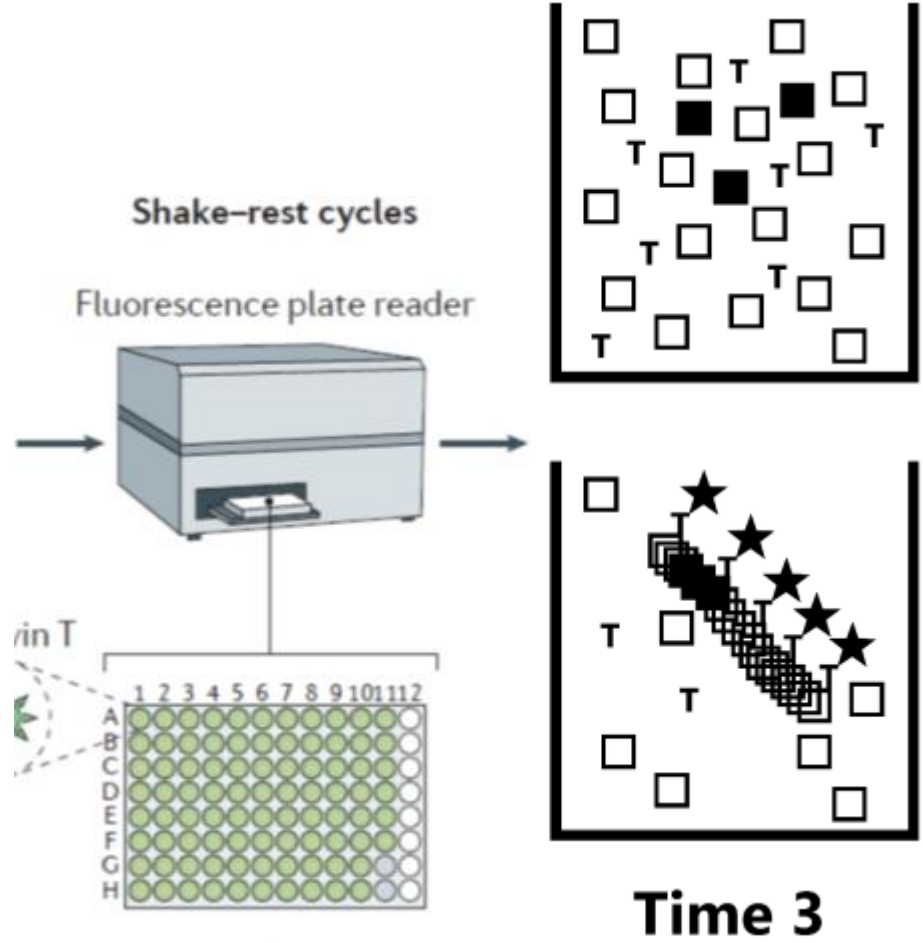
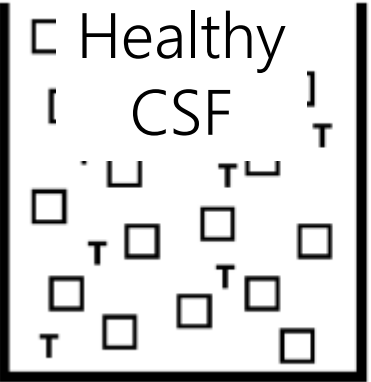


Negative

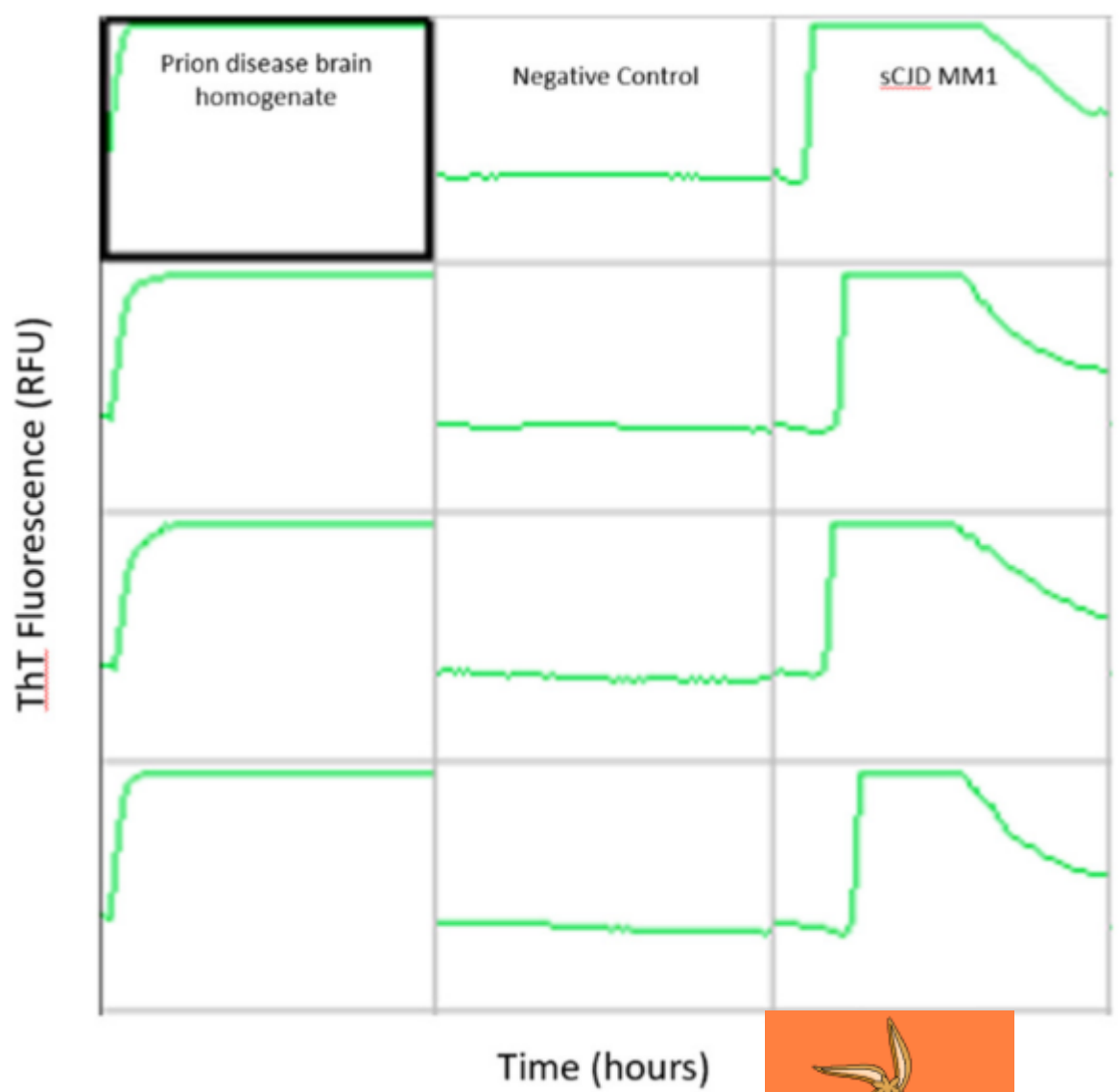
14-3-3 still sucks, and
clinicians still love it (bad)



Positive



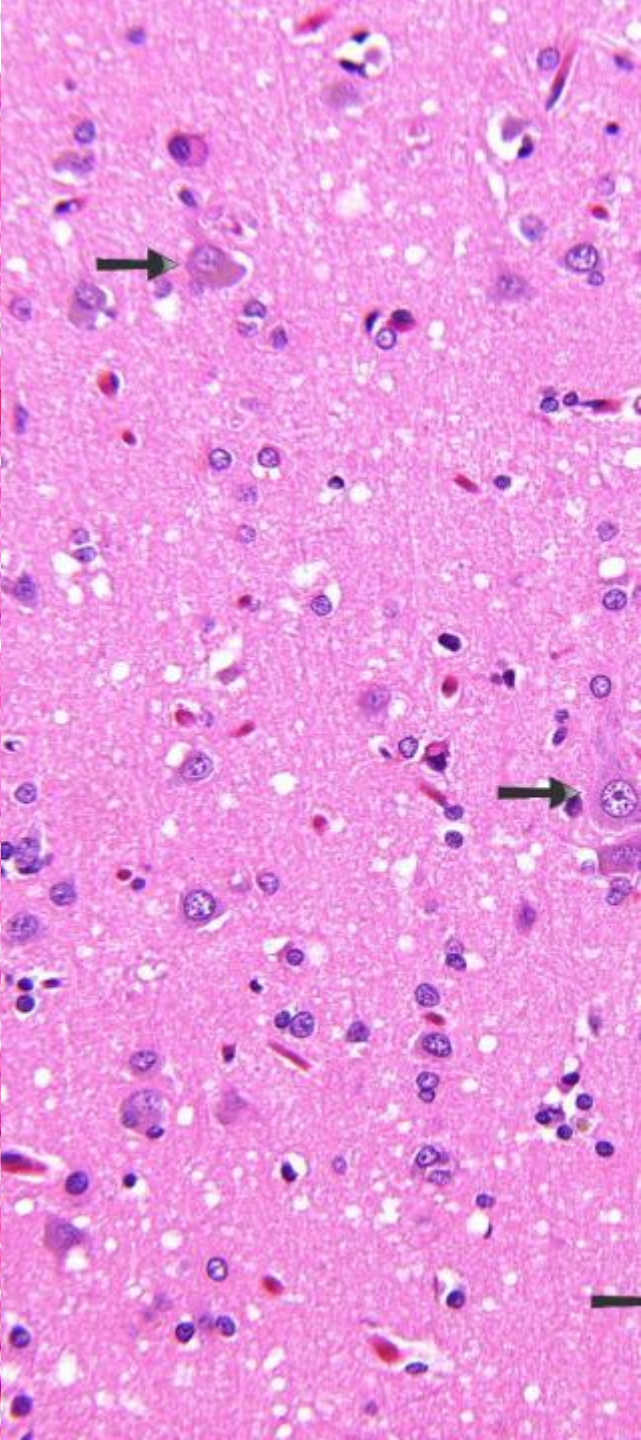
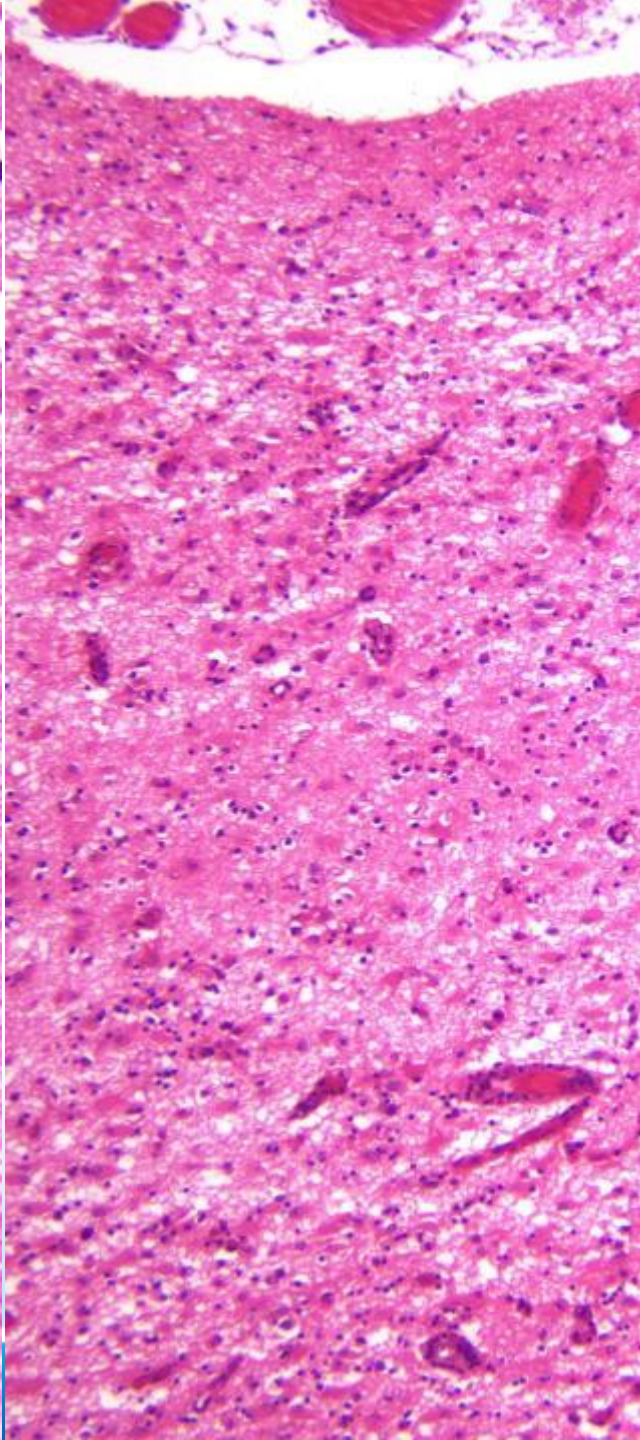
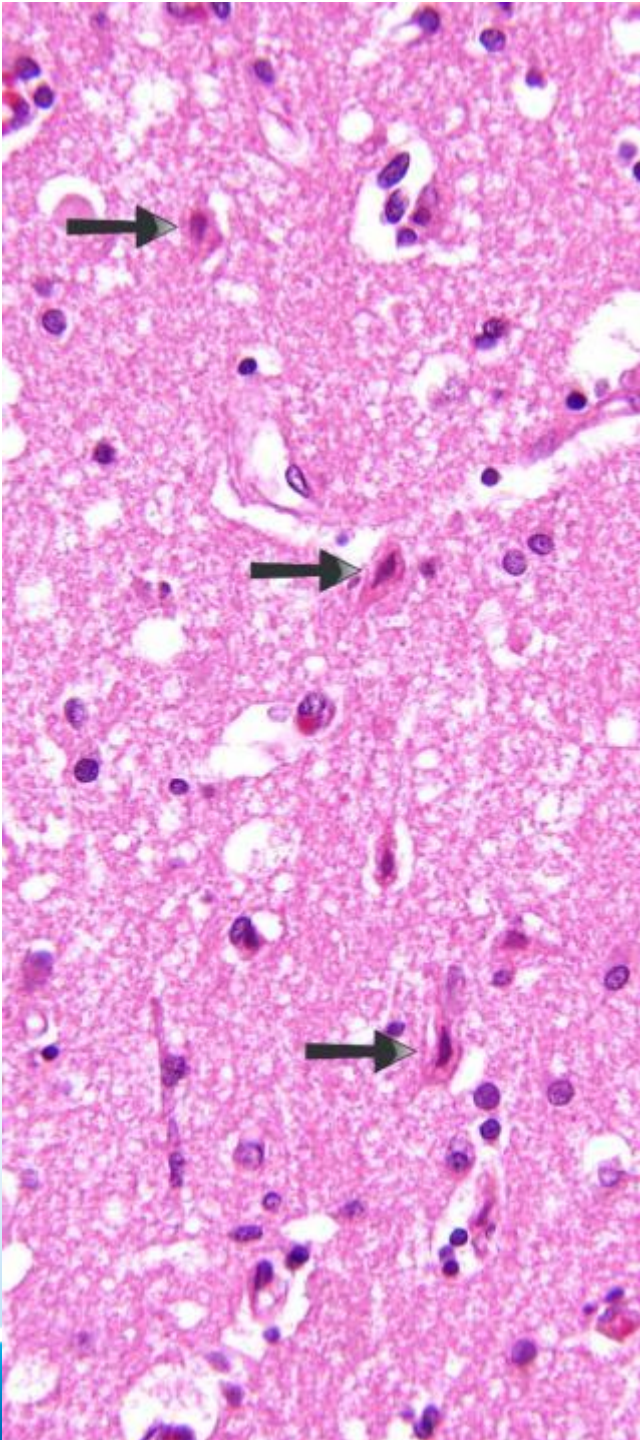
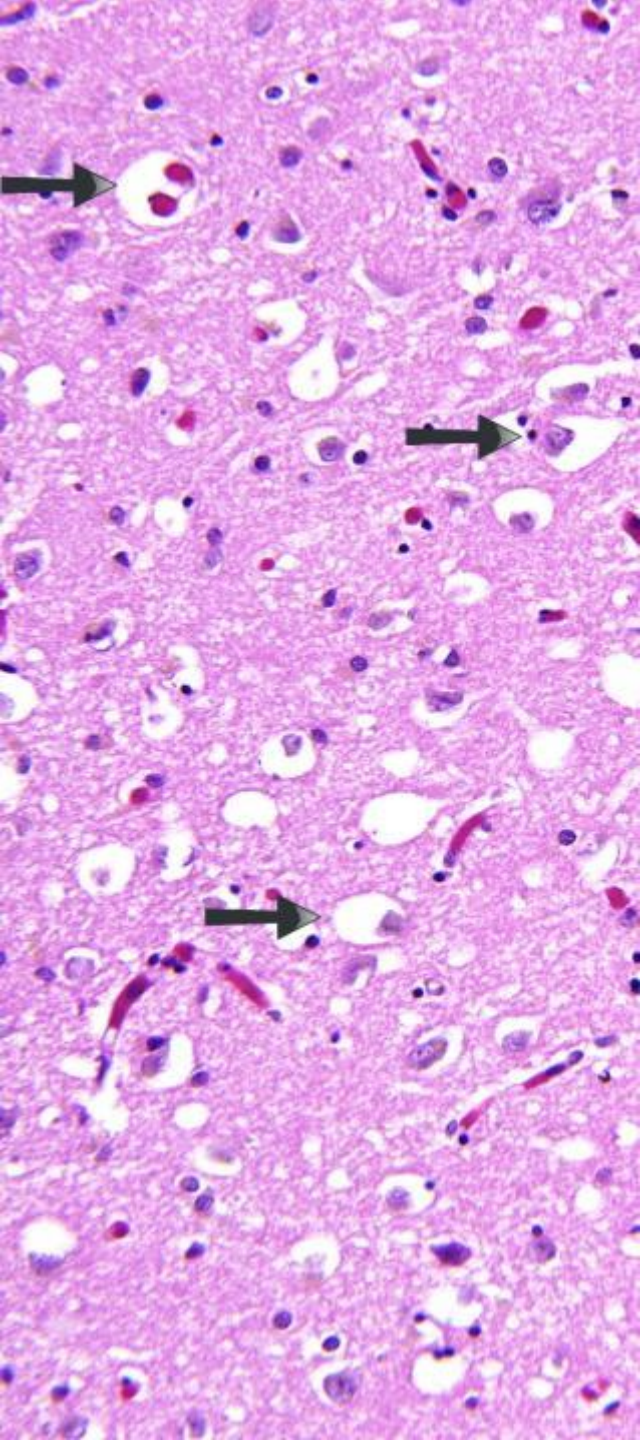
T	Thioflavin T that does not fluoresce	□	Reagent PrP
★	Thioflavin T capable of fluorescence	■	Cellular PrP from specimen
		■	Pathogenic PrP from specimen

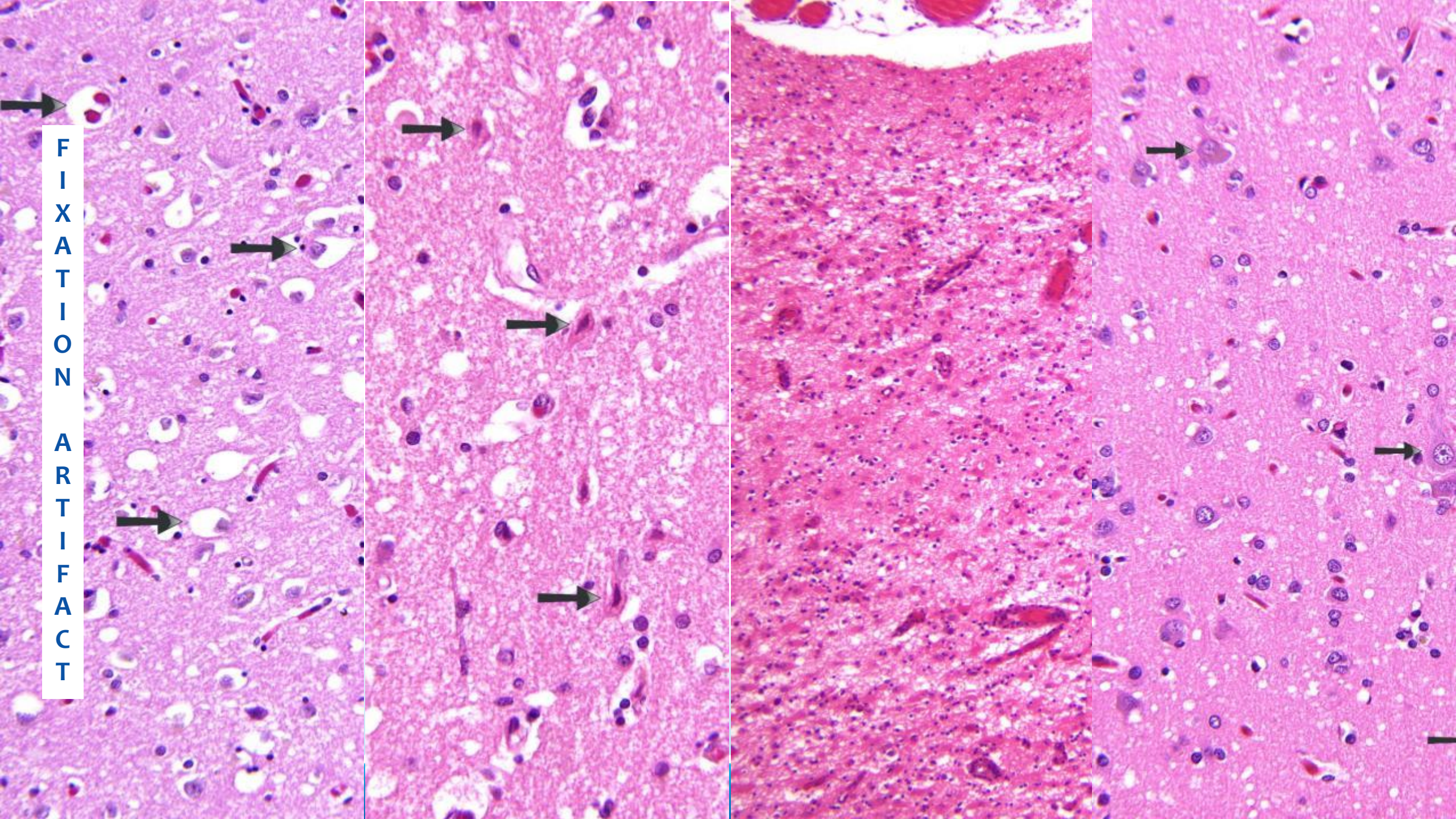


76-year-old man with progressive behavioral, cognitive, and visual dysfunction.

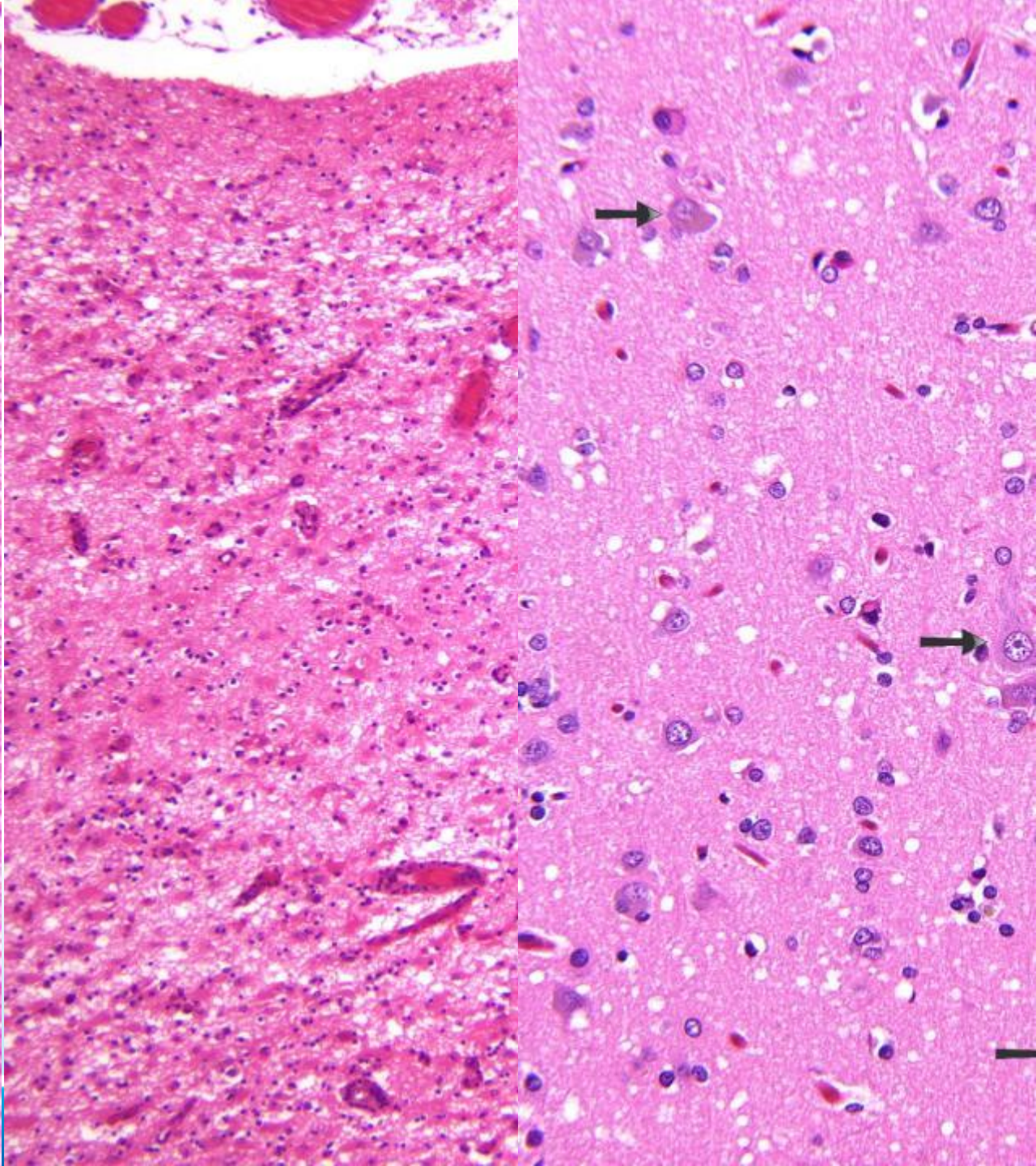
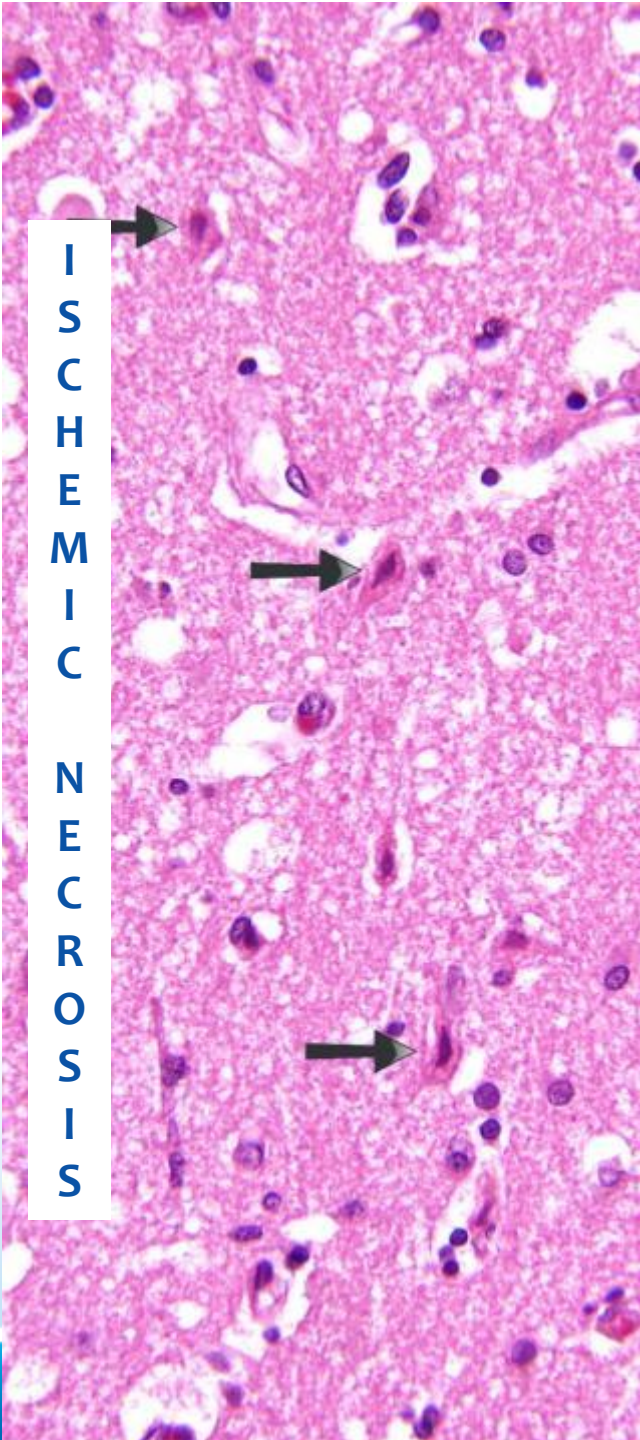
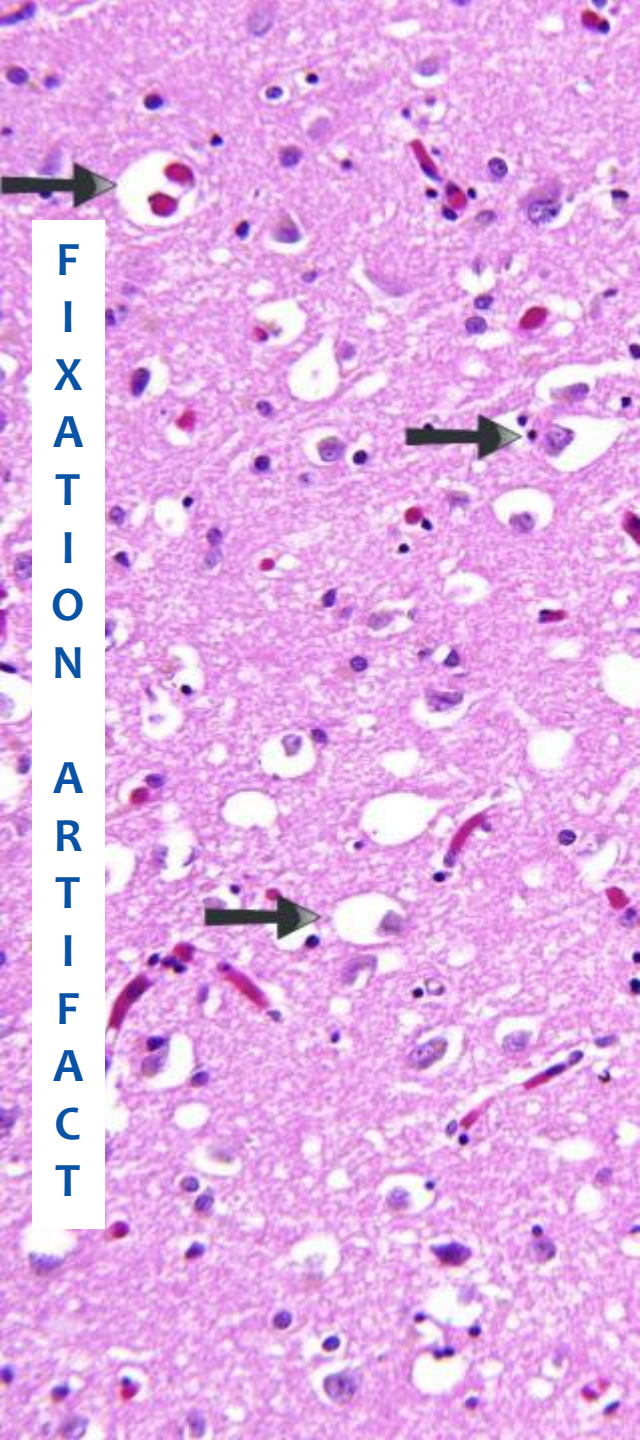
VM CASE (HORSES)

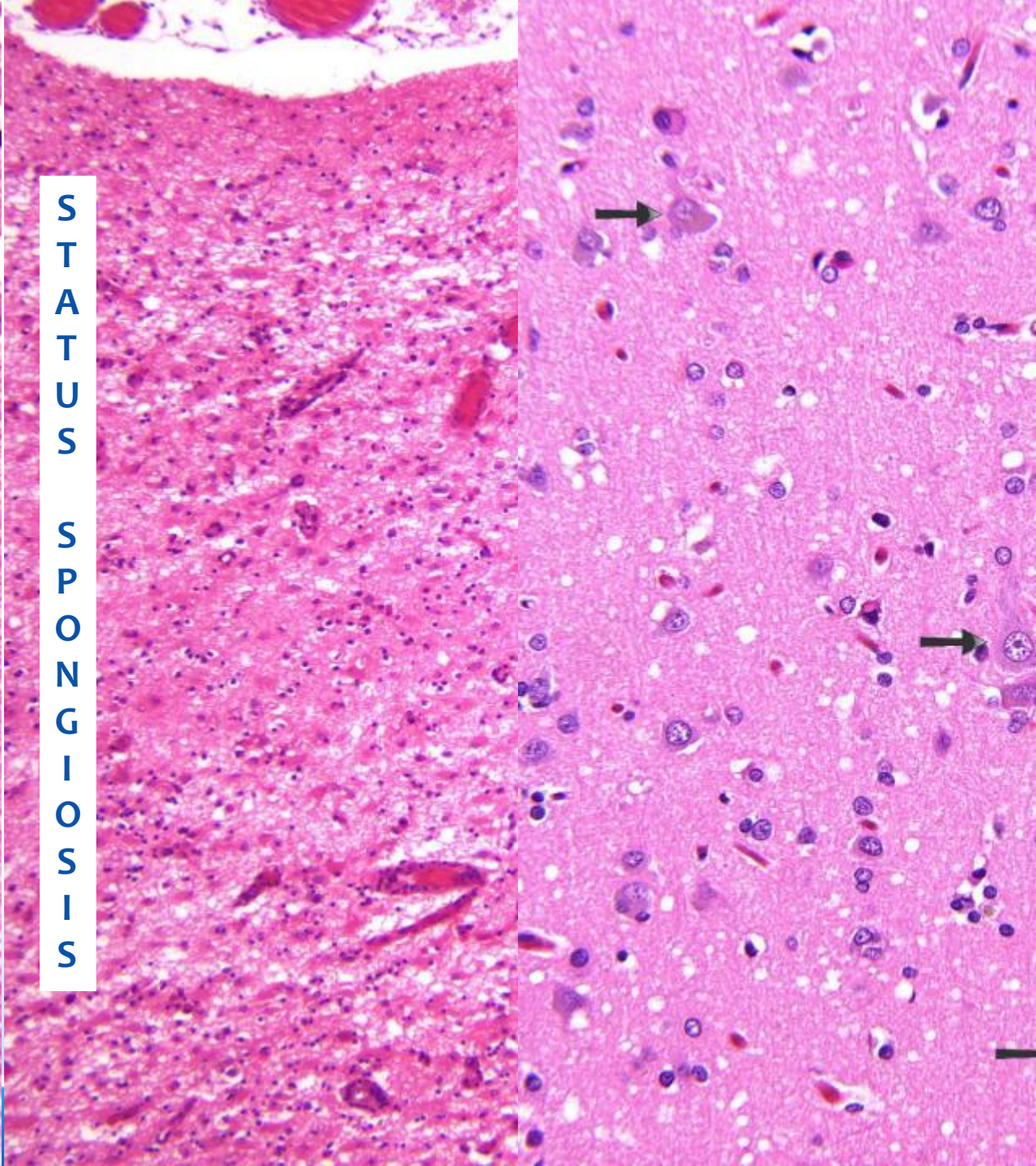
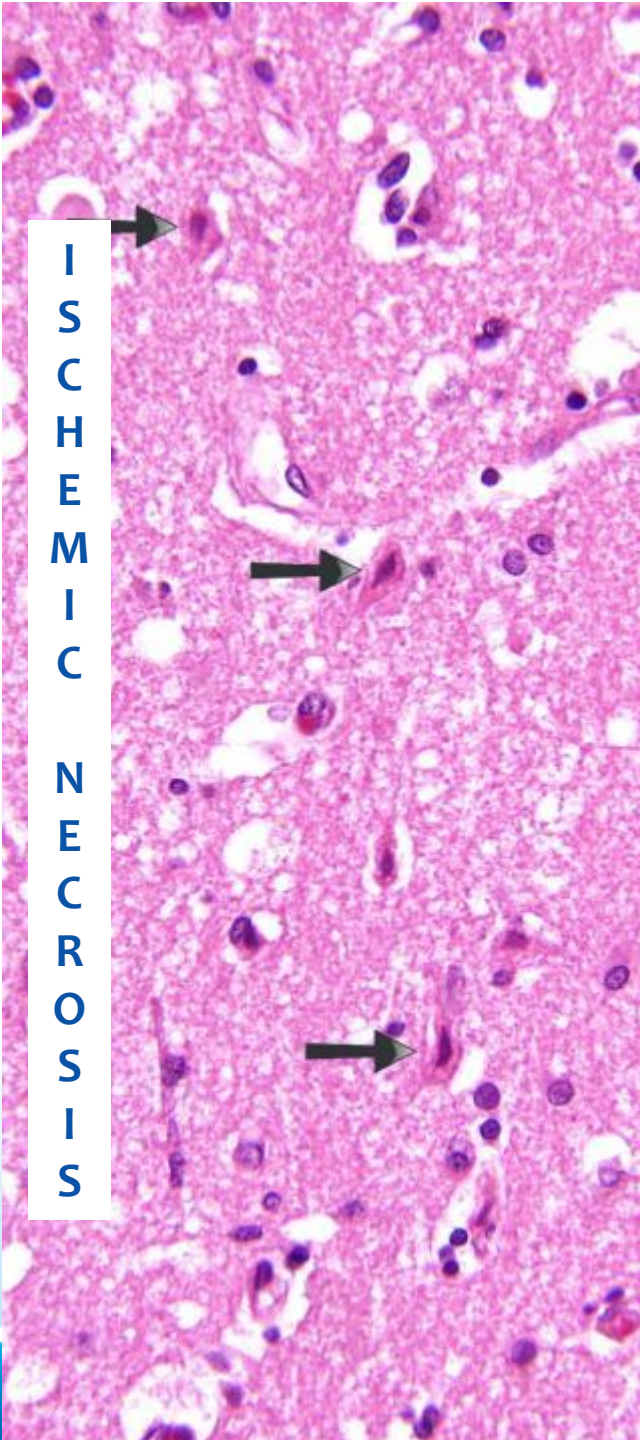
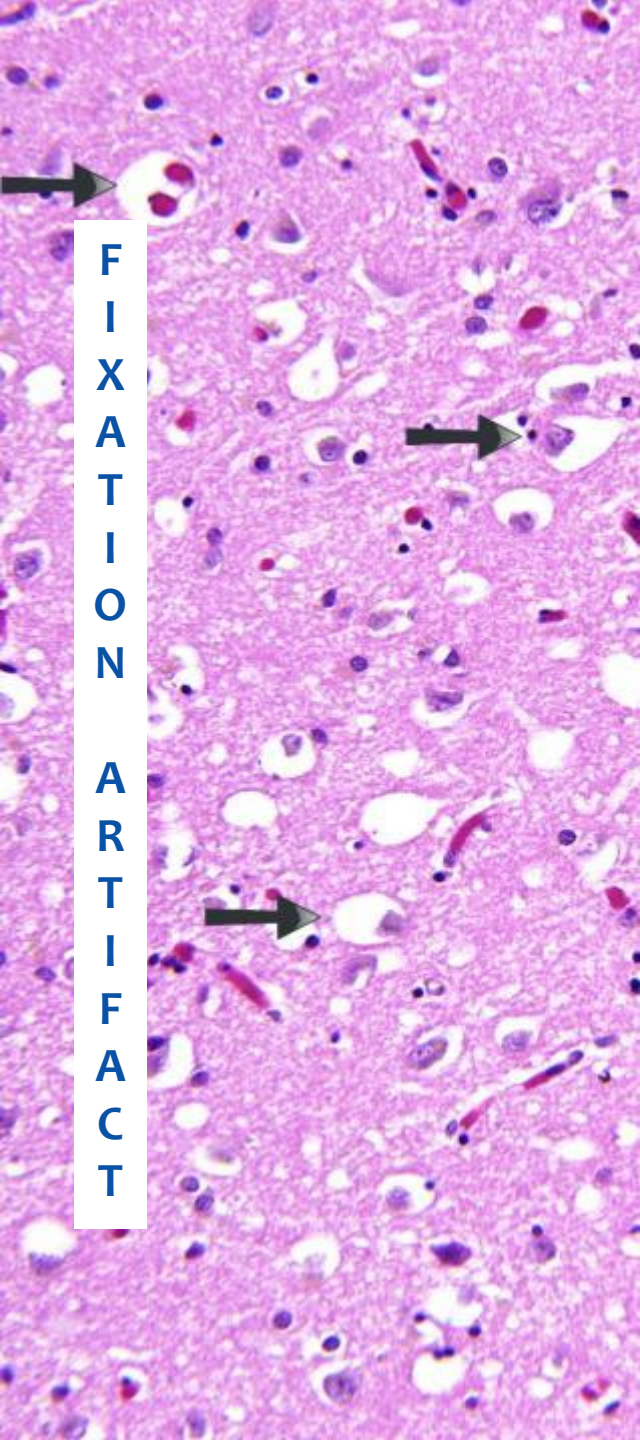


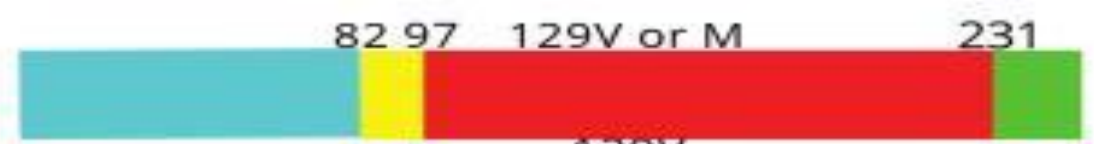




FIXATION
ARTIFACT





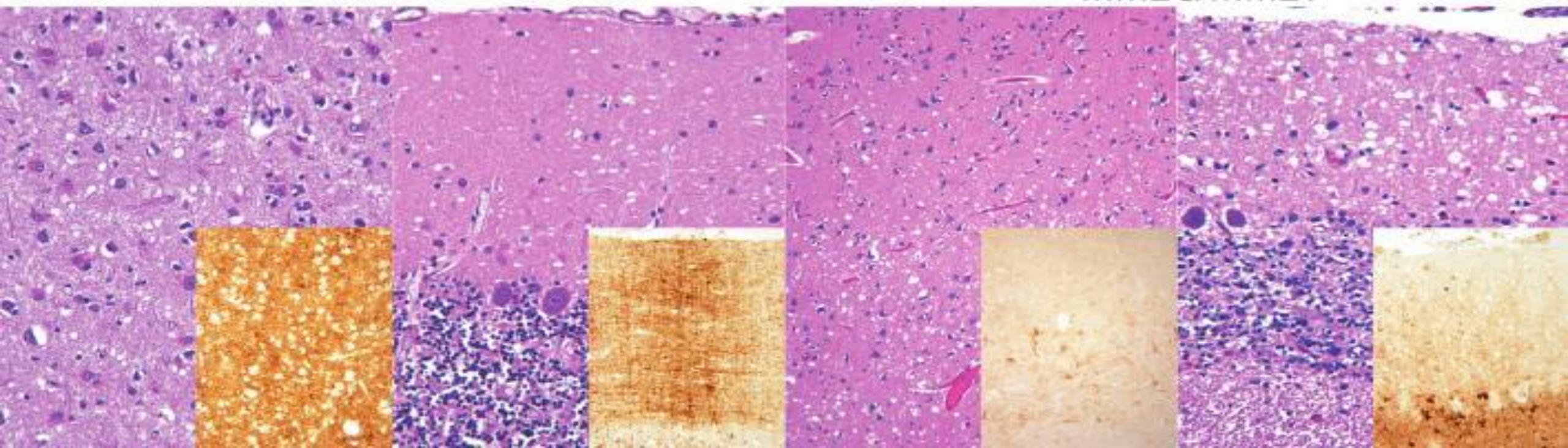


Proteinase K

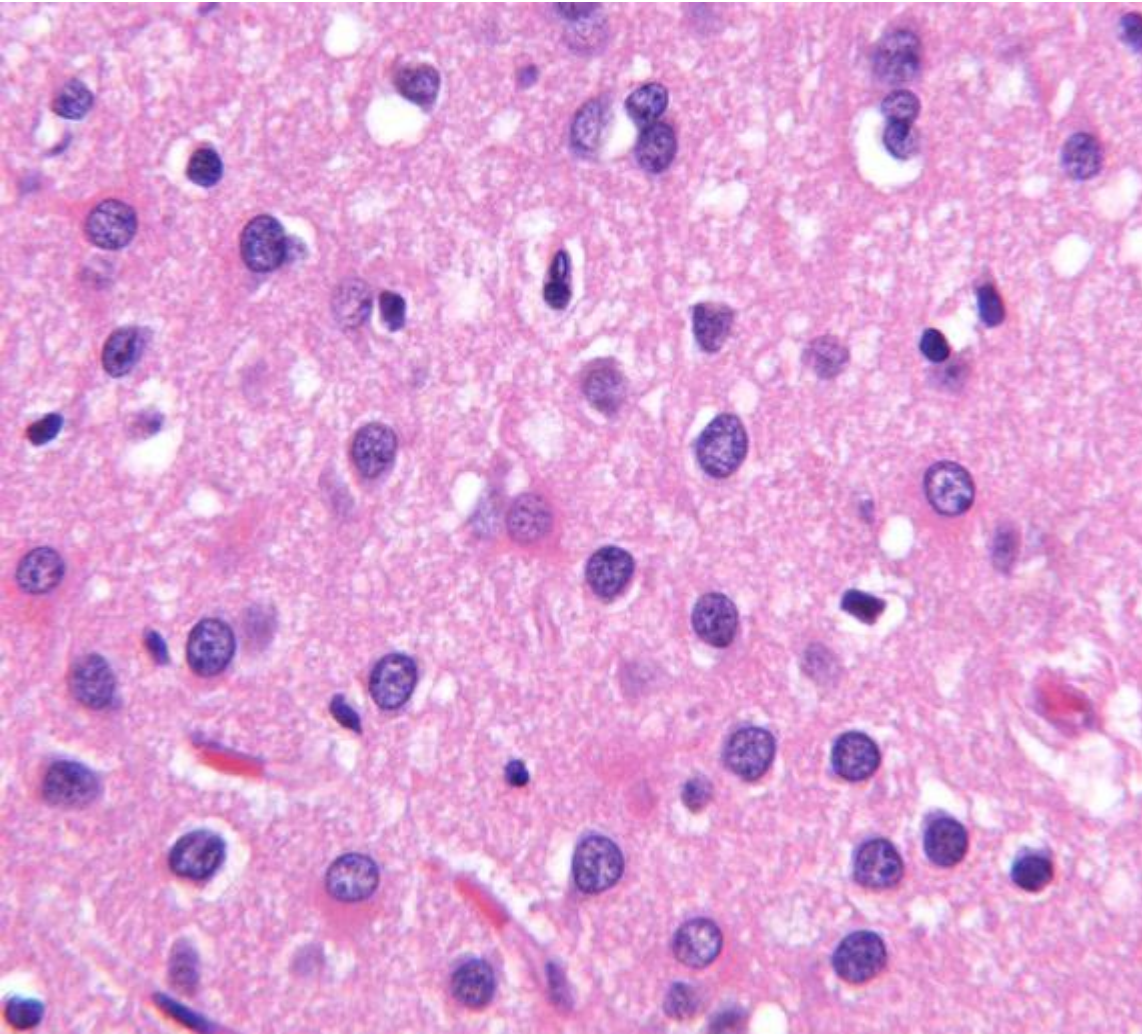


MM(MV)1
VV1

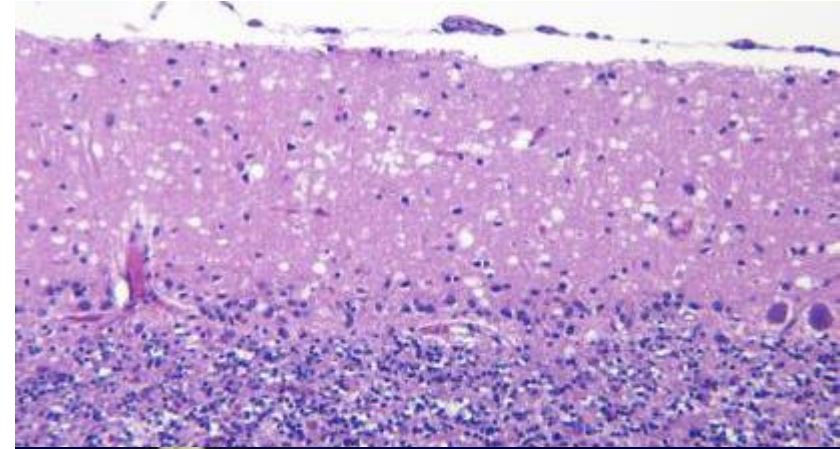
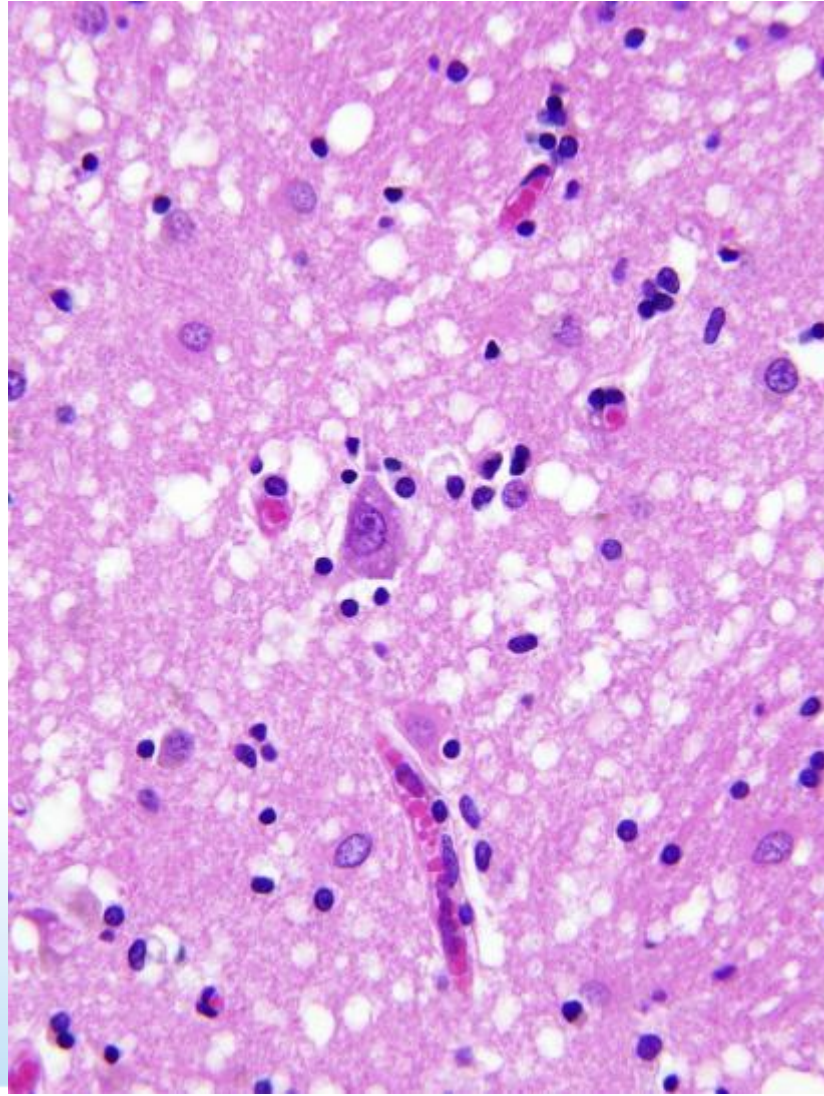
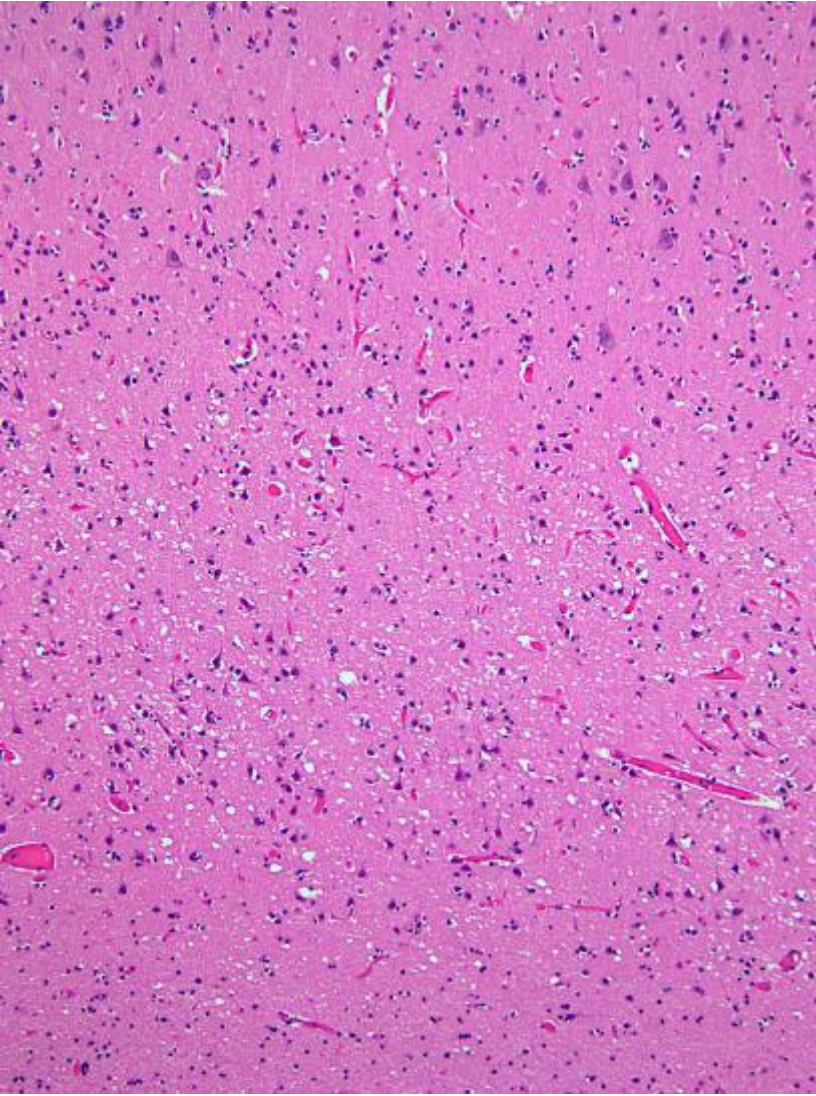
VV2/MV2
MM2C/MM2T



Classic (MM/V1) CJD shows fine vacuolation involving all cortical layers, with relative sparing of the hippocampus



Ataxic (V_{V2}) CJD shows deep laminar cortical vacuolation with marked striatal and cerebellar degeneration



58-year-old man with alcohol and drug abuse, two years of dizziness initiated by motion, and recent memory difficulties.

VM CASE 2 (ZEBRAS)

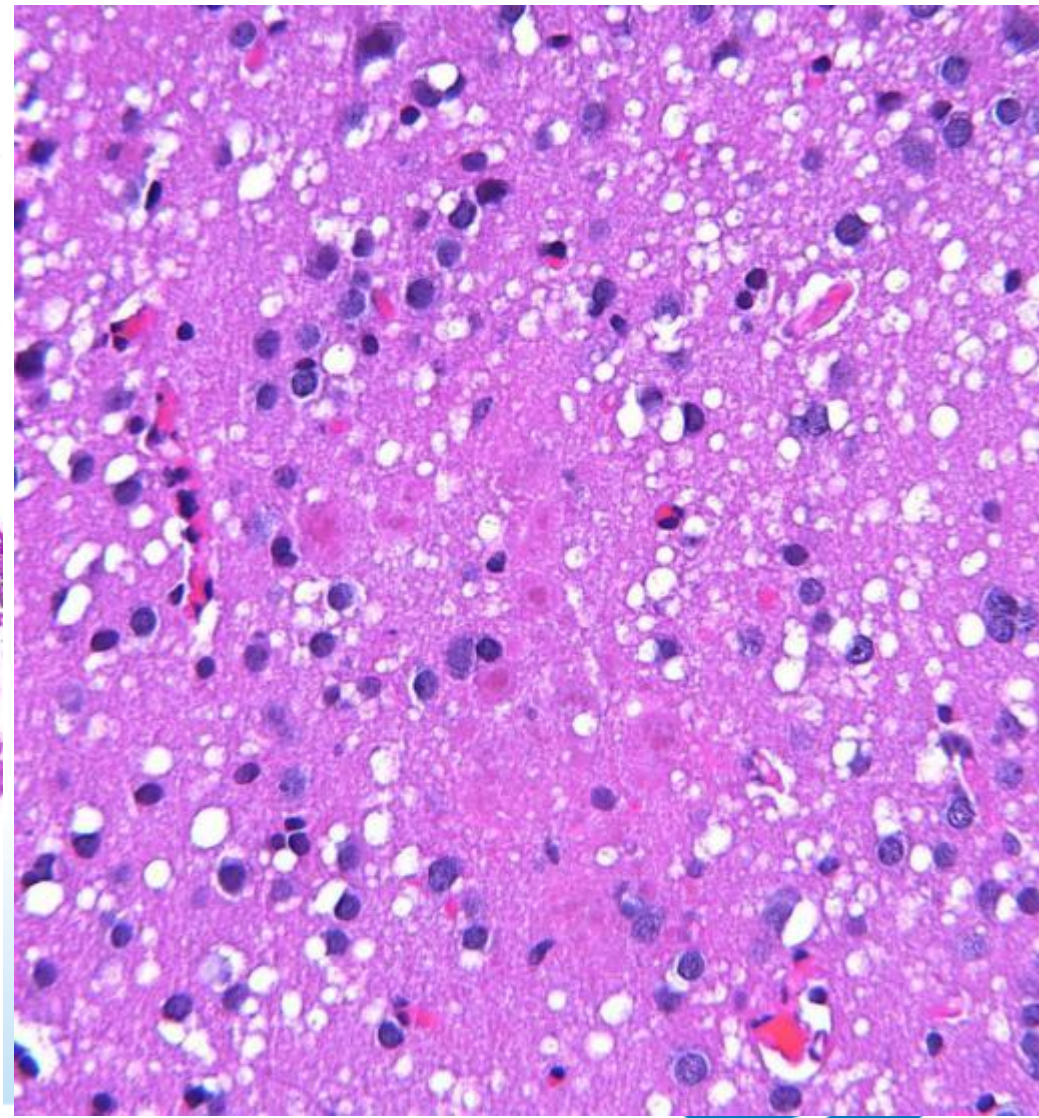
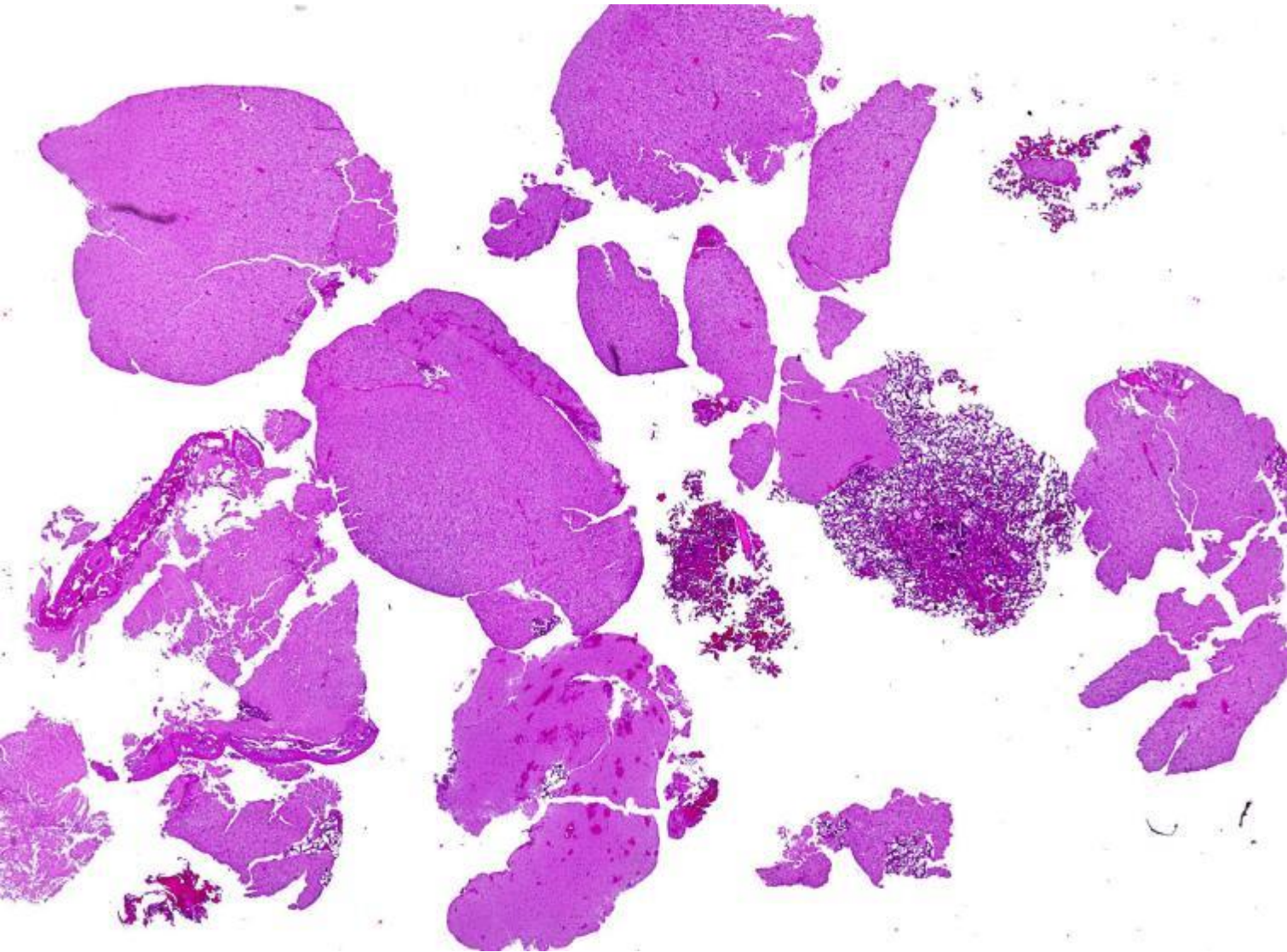


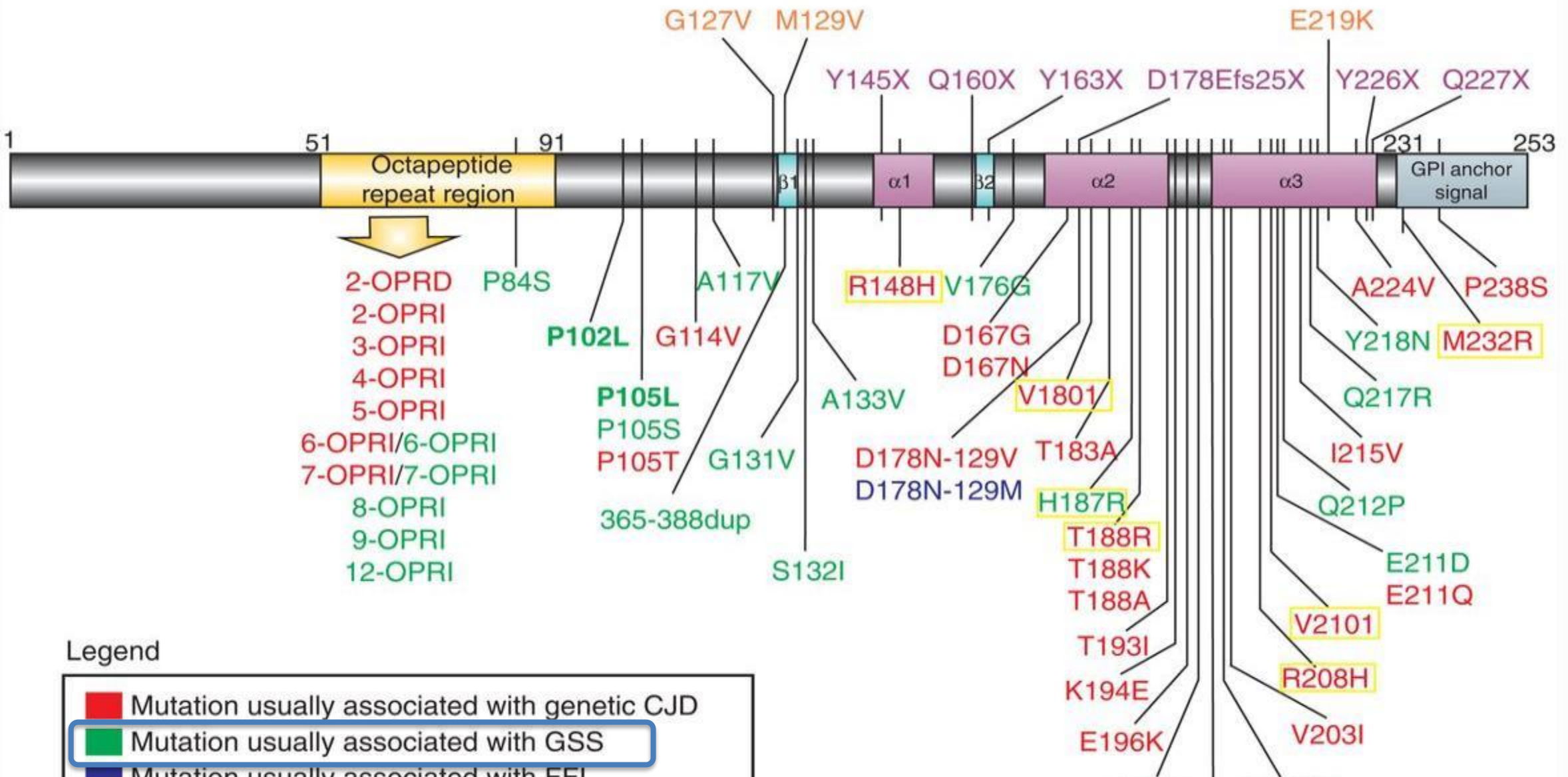
Sporadic CJD demonstrates *heterozygote advantage* with respect to the codon 129 polymorphism

Disease subtype	Relative frequency	Mean survival
MM1	65%	4 months
VV2	15%	6.5 months
MV2	10%	17 months



36-year-old woman with >5 years of brainstem and cerebellar dysfunction, now with cognitive decline. Father died from spinocerebellar ataxia.



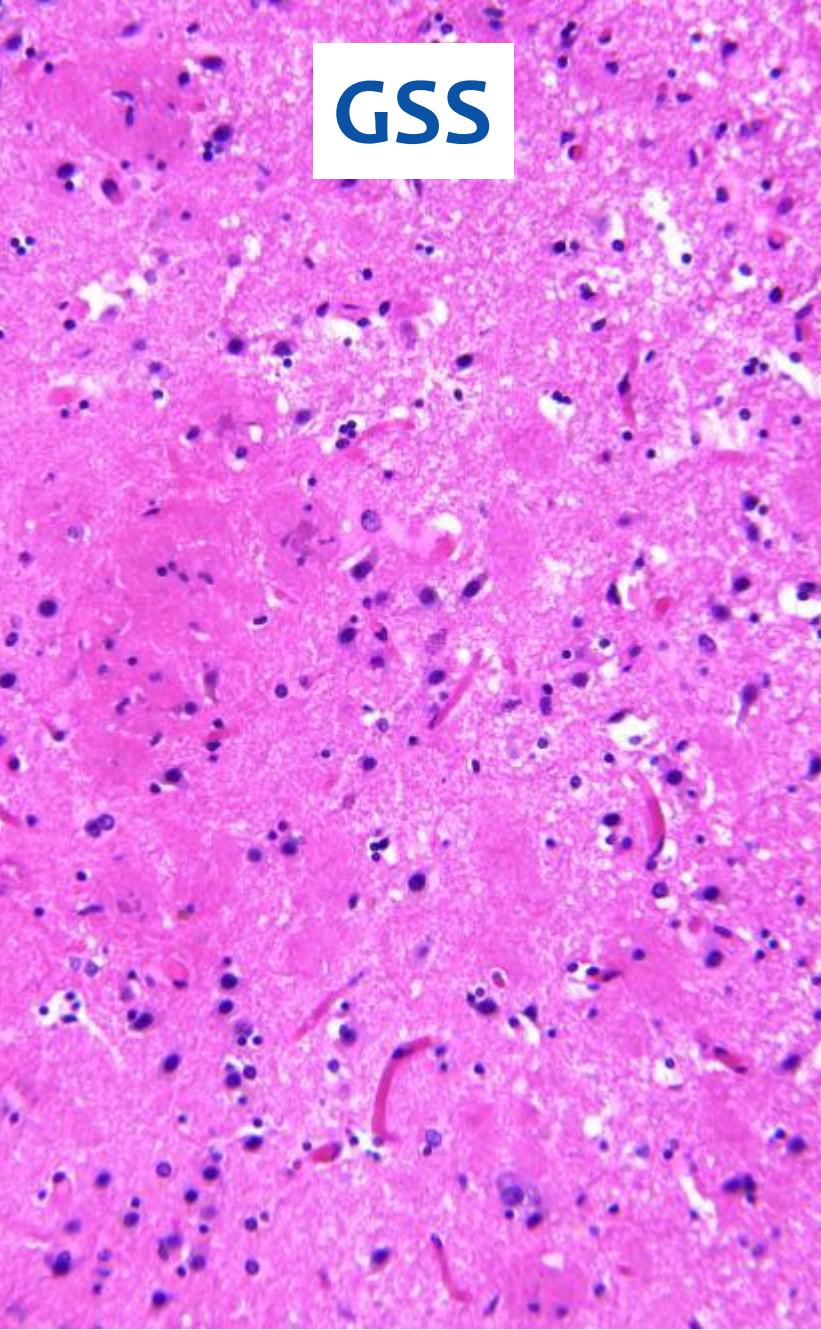


Legend

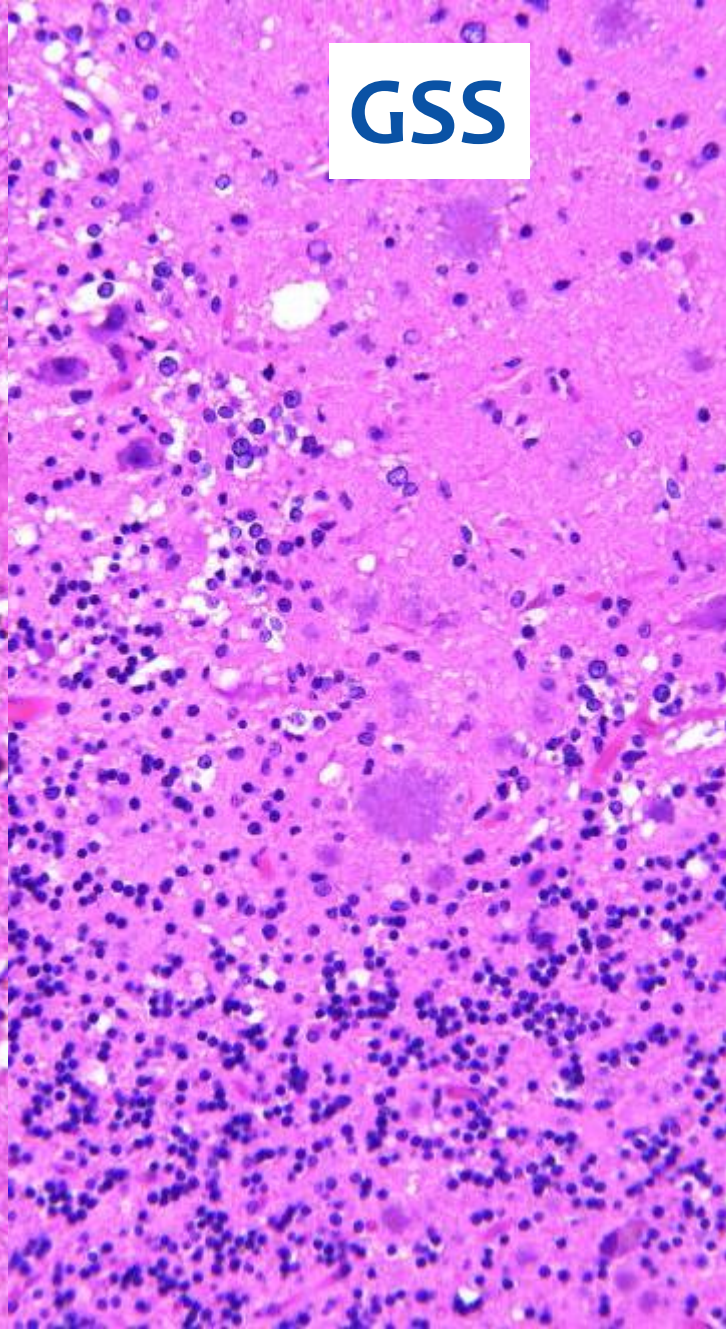
- Mutation usually associated with genetic CJD
- Mutation usually associated with GSS
- Mutation usually associated with FFI
- Nonsense mutation
- Risk polymorphism
- Low or intermediate penetrance variants

Kim MO, Takada LT, Wong K, Forner SA, Geschwind MD.
Genetic PrP Prion Diseases.
Cold Spring Harb Perspect Biol. 2018;10(5):a033134.

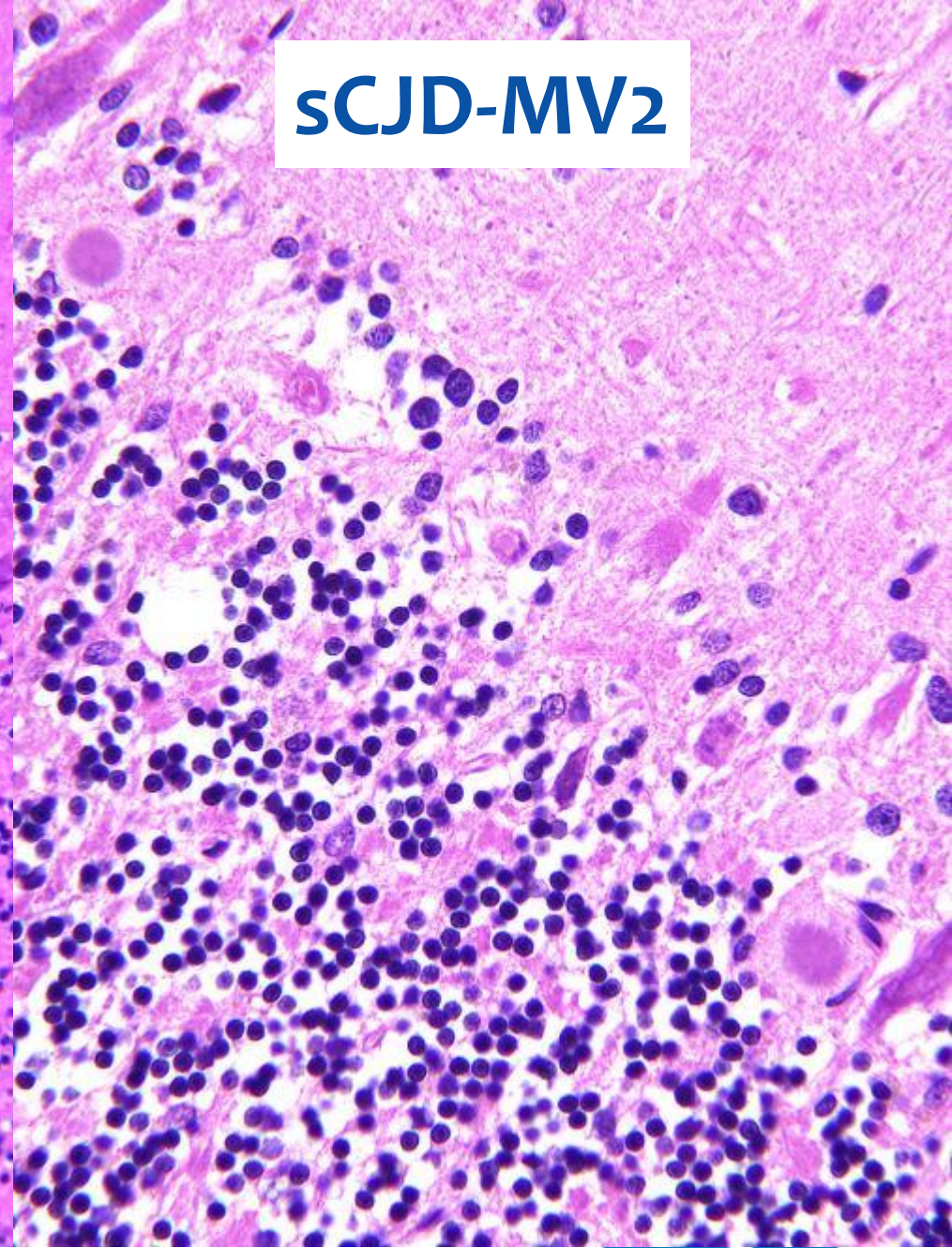
GSS



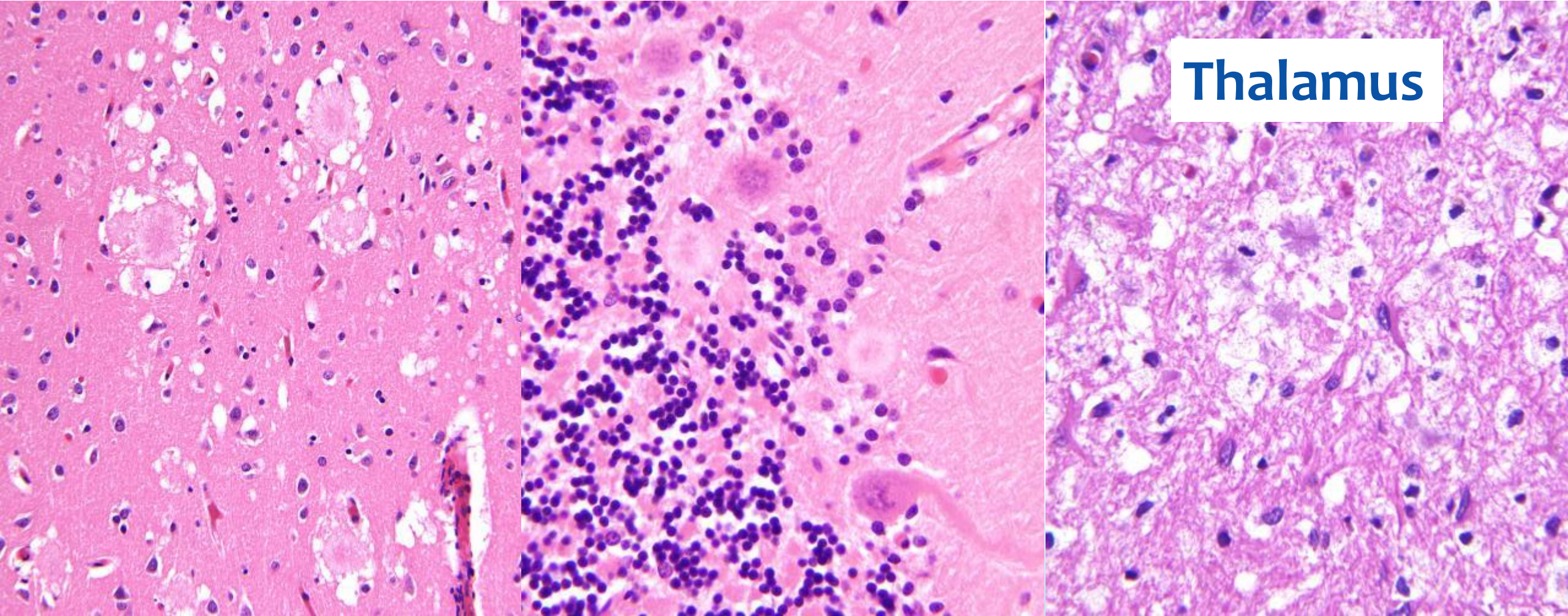
GSS



sCJD-MV2



27-year-old consumer of “Vintage British Beef” with 14 months of cognitive decline



Thalamus

33-year-old man who developed anxiety followed by double vision, gait difficulties, nocturnal panic attacks with trouble sleeping, memory problems, dysphagia, and myoclonus.

VM CASE 3 (UNICORNS)



“A physician has got to know his limitations”

--Dr. C. Eastwood

- Insomnia is not a defining feature of Fatal Insomnia
- MRI & EEG can be normal
- RT-QuIC is often negative
- Brain biopsy will be negative
- Autopsy will be negative if thalamus and medulla not examined
- Polysomnography may support the diagnosis
- PrP IHC may be positive in the medial temporal lobe
- Western blot is often diagnostic



When Prions escape – WTF do I do now?

Creutzfeldt-Jakob Disease, Classic (CJD)

CDC > Prion Diseases > CJD

Home CJD

About CJD

Clinical and Pathologic Characteristics

Diagnostic Criteria

Infection Control

Information for Funeral and Crematory Practitioners

Occurrence and Transmission

Treatment

Resources

Infection Control

DON'T PANIC

Iatrogenic transmission of CJD...
The CJD agent has been identified in over 500...
These cases have been linked to the use of contaminated human growth hormone, dura mater, and corneal grafts, or neurosurgical equipment. Six patients were associated with neurosurgical instruments, and two with stereotactic EEG depth electrodes.

All of these equipment-related cases occurred before the routine implementation of sterilization procedures currently used in health care facilities.

No such cases have been reported since 1976, and no iatrogenic CJD cases associated with exposure to the CJD agent from surfaces such as floors, walls, or countertops have been identified.

Reprocessing Surgical Instruments Used on Suspected or Confirmed CJD Patients

Inactivation studies have not rigorously evaluated the effectiveness of actual cleaning and reprocessing methods used in health care facilities.

Recommendations to reprocess instruments potentially contaminated with the CJD agent are primarily derived from in vitro inactivation studies that used either brain tissues or tissue homogenates, both of which pose enormous challenges to any sterilization process.

No iatrogenic CJD cases associated with exposure to the CJD agent from surfaces such as floors, walls, or countertops have been identified

[Autoclave Sterilization Methods Outlined in WHO Guidelines](#)

[Reprocessing Instruments used in Patients with no Clear Diagnosis of CJD](#)

[Decontaminating Heat-sensitive Instruments or Materials](#)

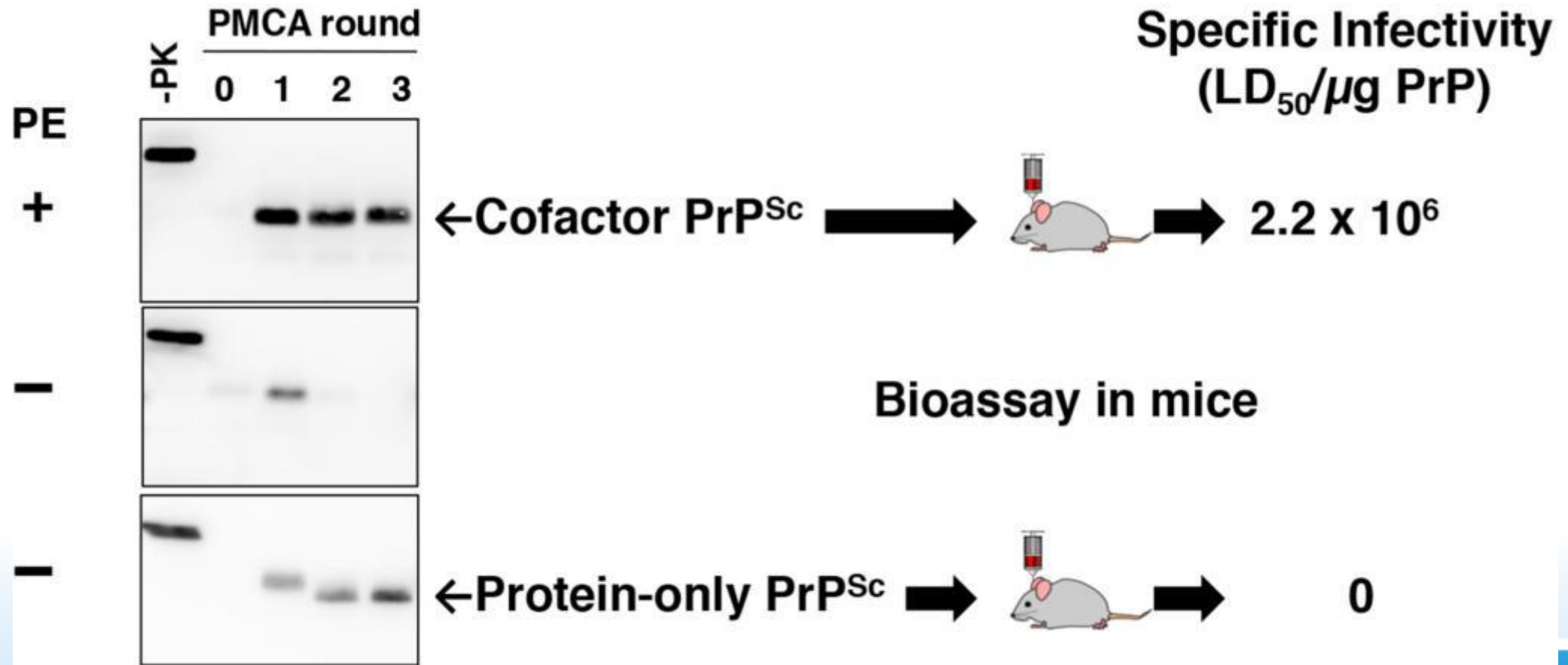
[Precautions for Embalming the Bodies of Patients with Suspected or Confirmed CJD](#)

Related Links

[Prion Diseases](#)



Give me one good reason I shouldn't freak out, and not just that it hasn't been reported



Supattapone S. Cofactor molecules: Essential partners for infectious prions. *Prog Mol Biol Transl Sci.* 2020;175:53-75.



Not good enough. How about some human data that I can share with my laboratory personnel?

Table 3. Inoculation of sCJD CSF samples into Tg66 mice.

Donor	Inoculum dilution	Clinical prion disease (+/total)	Survival time dpi (mean +/- SD)	Neuropathology and PrP IHC (+/total tested)	RT-QuIC (+/ total tested)
sCJD Patient 1	1:1	0/6	556 +/-56	0/5	0/5
	1:20	0/6	616 +/-64	NT	0/4
sCJD Patient 2	1:1	0/6	547 +/-74	NT	0/4
	1:20	0/5	657 +/-40	NT	0/3
sCJD Patient 8	1:1	0/5	528 +/-89	0/2	0/4
	1:20	0/5	587 +/-13	NT	0/2
Non-CJD	1:1	0/6	550 +/-73	0/3	0/5

NT: not tested.

Raymond GJ, Race B, Orrú CD, et al. Transmission of CJD from nasal brushings but not spinal fluid or RT-QuIC product. *Ann Clin Transl Neurol.* 2020;7(6):932-944.

Table 4. Inoculation of sCJD-seeded RT-QuIC products into Tg66 mice.

RT-QuIC product inoculum	Total PrP inoculated	Clinical prion disease (+/total)	Survival time dpi (mean +/- SD)	Atypical neuropathology and PrP IHC ¹ (+/total tested)	RT-QuIC (+/ total tested)
CJD Patient 2-seeded	5 µg	0/5	644 +/- 7	4/4	2/2
	0.5 µg	0/6	554 +/-104	2/3	NT
CJD Patient 8-seeded	5 µg	0/5	560 +/- 62	2/2	1/1
	0.5 µg	0/6	624 +/-53	6/6	3/3
Control Patient-seeded	2.5 µg	0/4	526 +/-36	0/4	0/4

NT: not tested. IHC: immunohistochemistry.

¹ Although abnormal vacuolation and PrP deposition were observed in the brains designated as positive in this column, these features differed markedly from those seen with any bona fide prion disease in this mouse model.



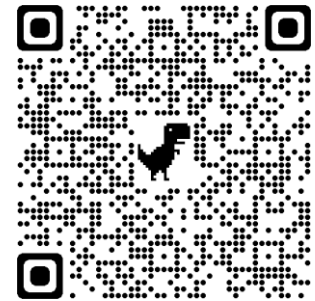
Minimise transmission risk of CJD and vCJD in healthcare settings

Prevention of CJD and vCJD by the Advisory Committee on Dangerous Pathogens' Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup.

From: [Department of Health and Social Care](#)

Published 27 November 2012

Last updated 18 November 2021 — [See all updates](#)



<https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group>



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