MAYO CLINIC

Diagnostic Slide Session at the 97th Annual Meeting of the American Association of Neuropathologists

Case 7

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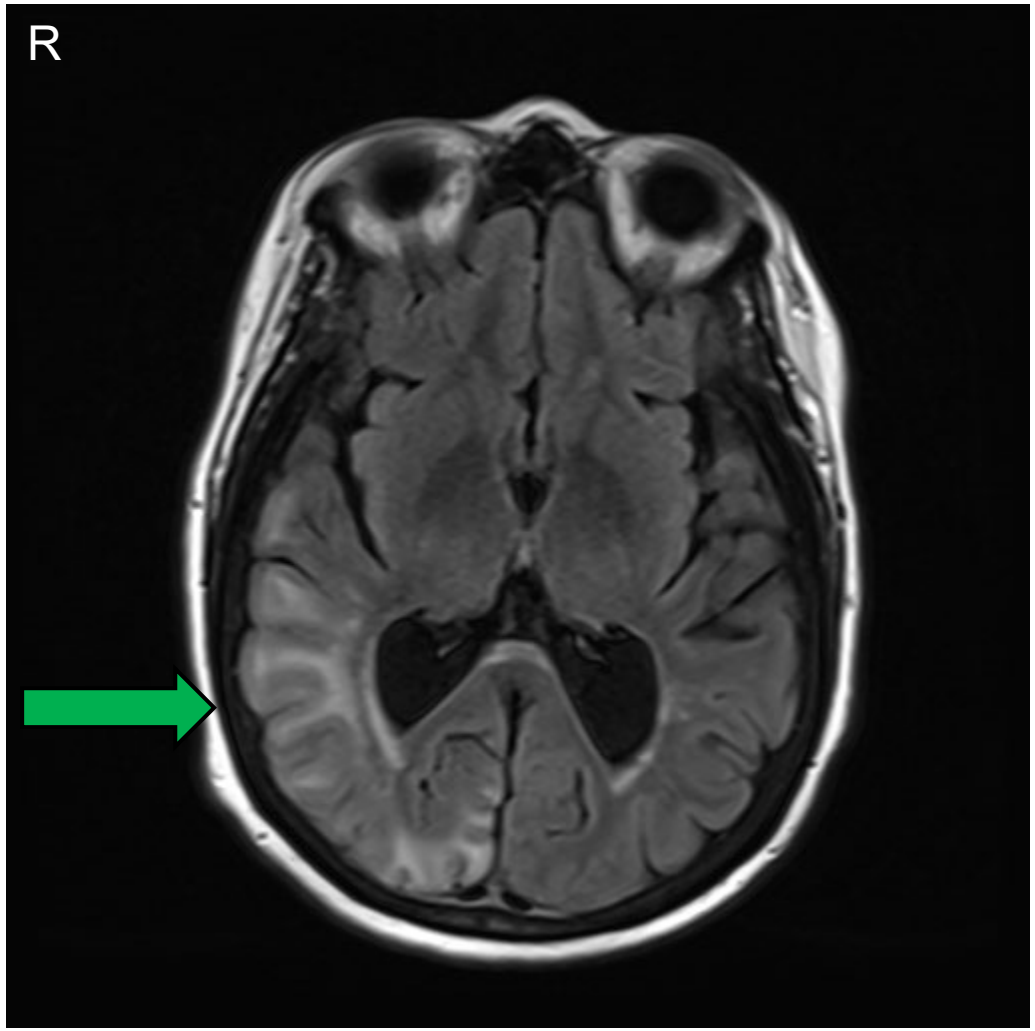
Clinical Summary

- 65-year-old woman with history of:
  - Essential tremor
  - Subacute cognitive decline: ataxia, aphasia, confusion, hallucinations
  - Left visual field loss
  - Brother began experiencing similar symptoms
- Extensive clinical work-up:
  - Unrevealing Cerebrospinal fluid (CSF) studies, cerebral angiogram, MRI spectroscopy, and electroencephalogram
  - 2015: right parietal-occipital brain biopsy
  - 2017: both siblings underwent skin biopsy
- Died after 10-years disease duration



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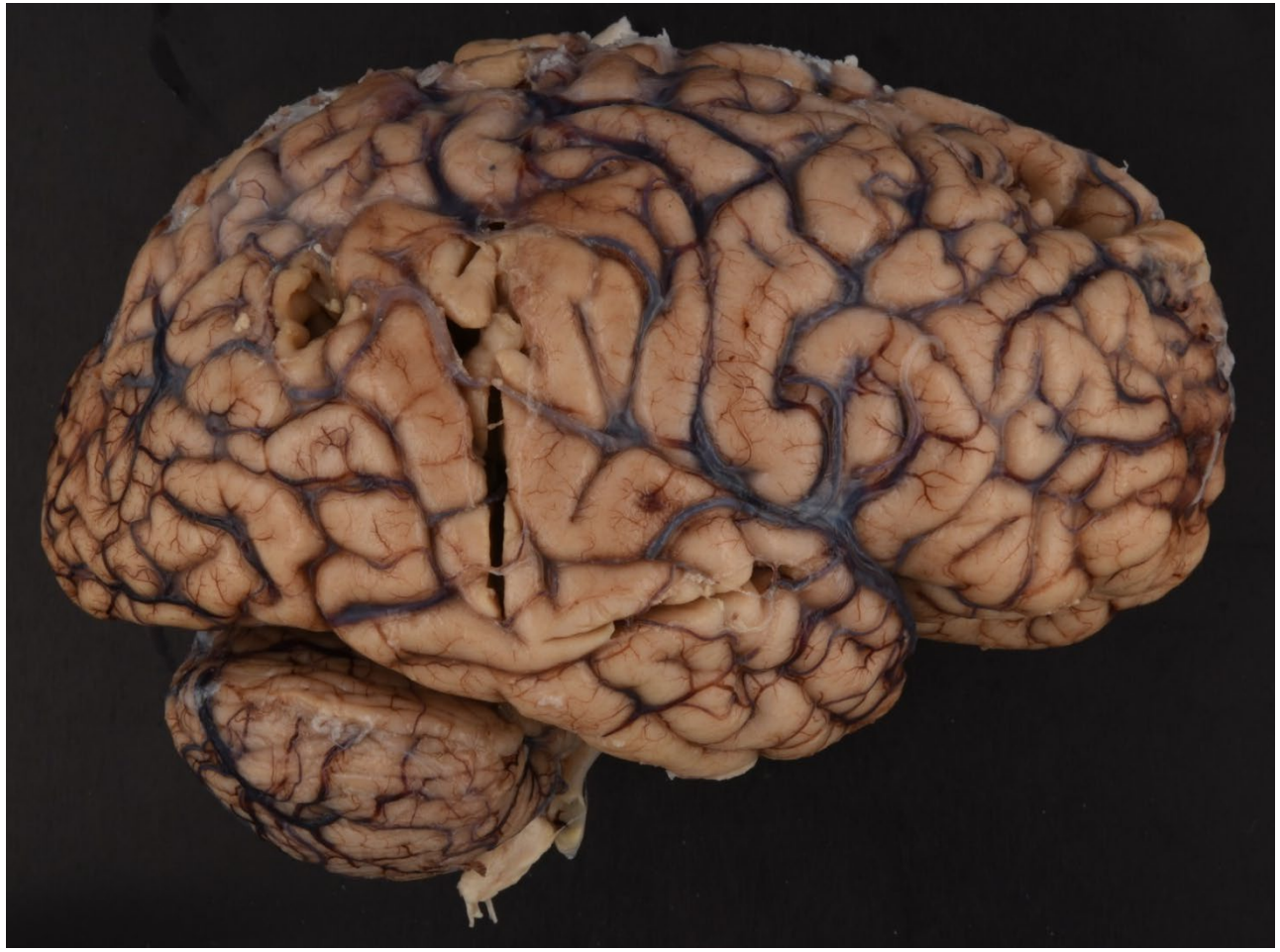
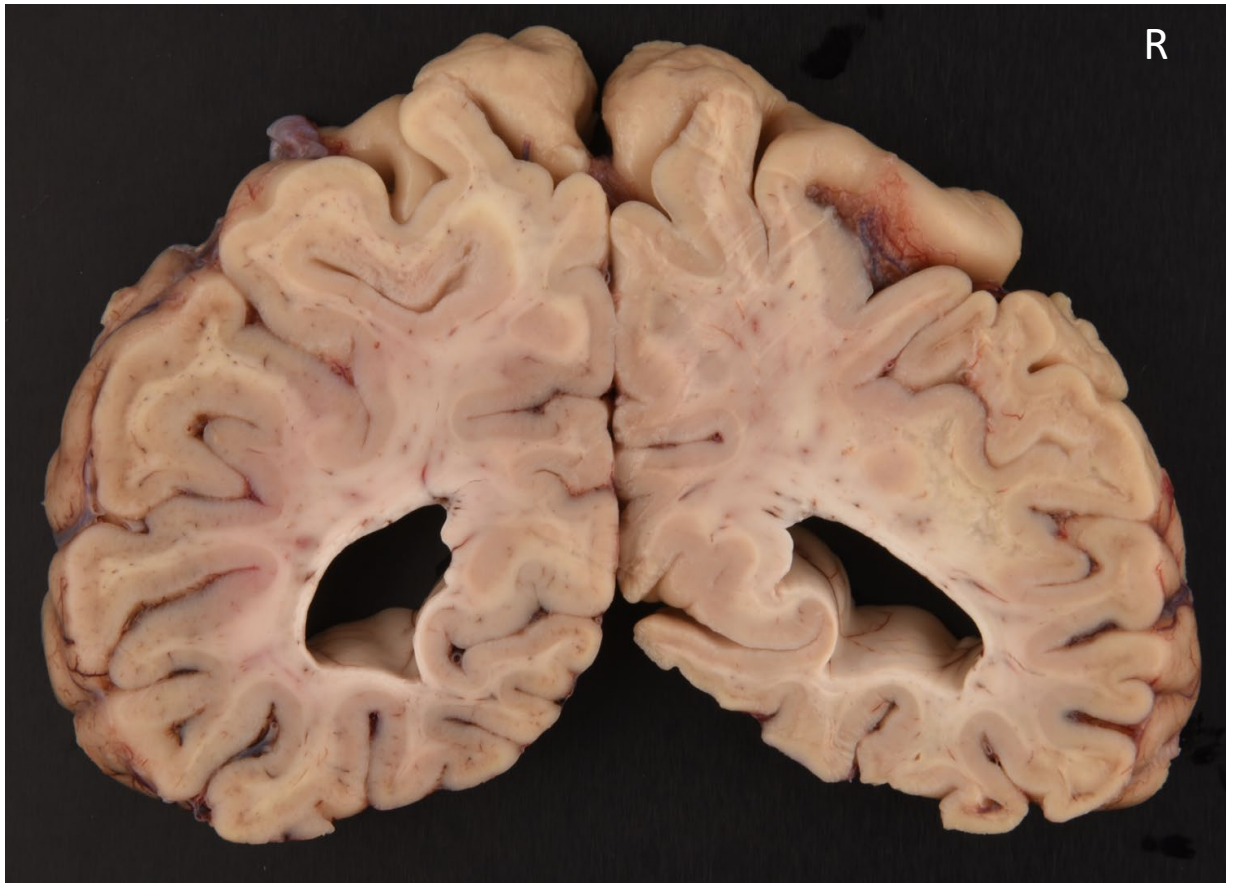
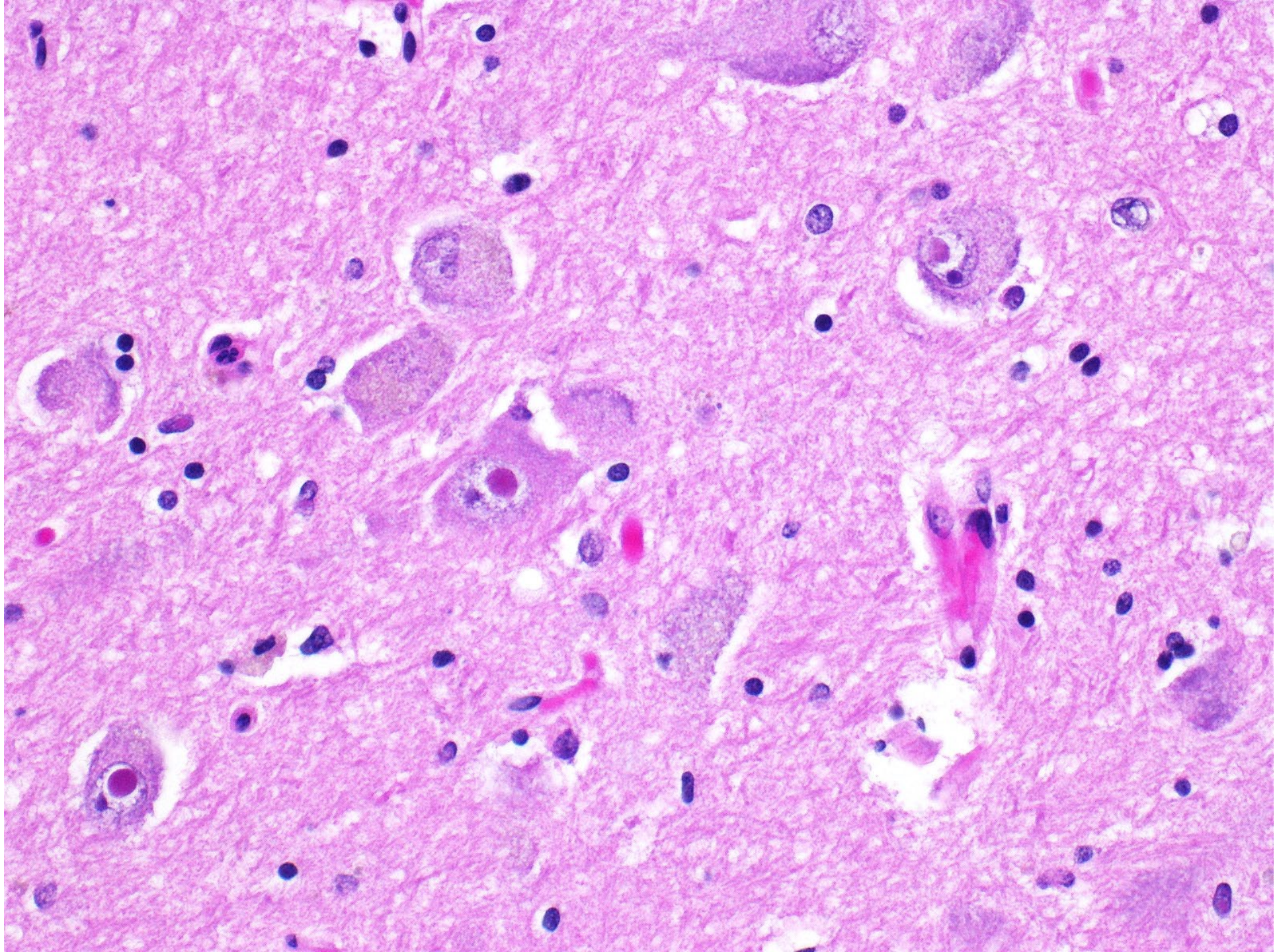
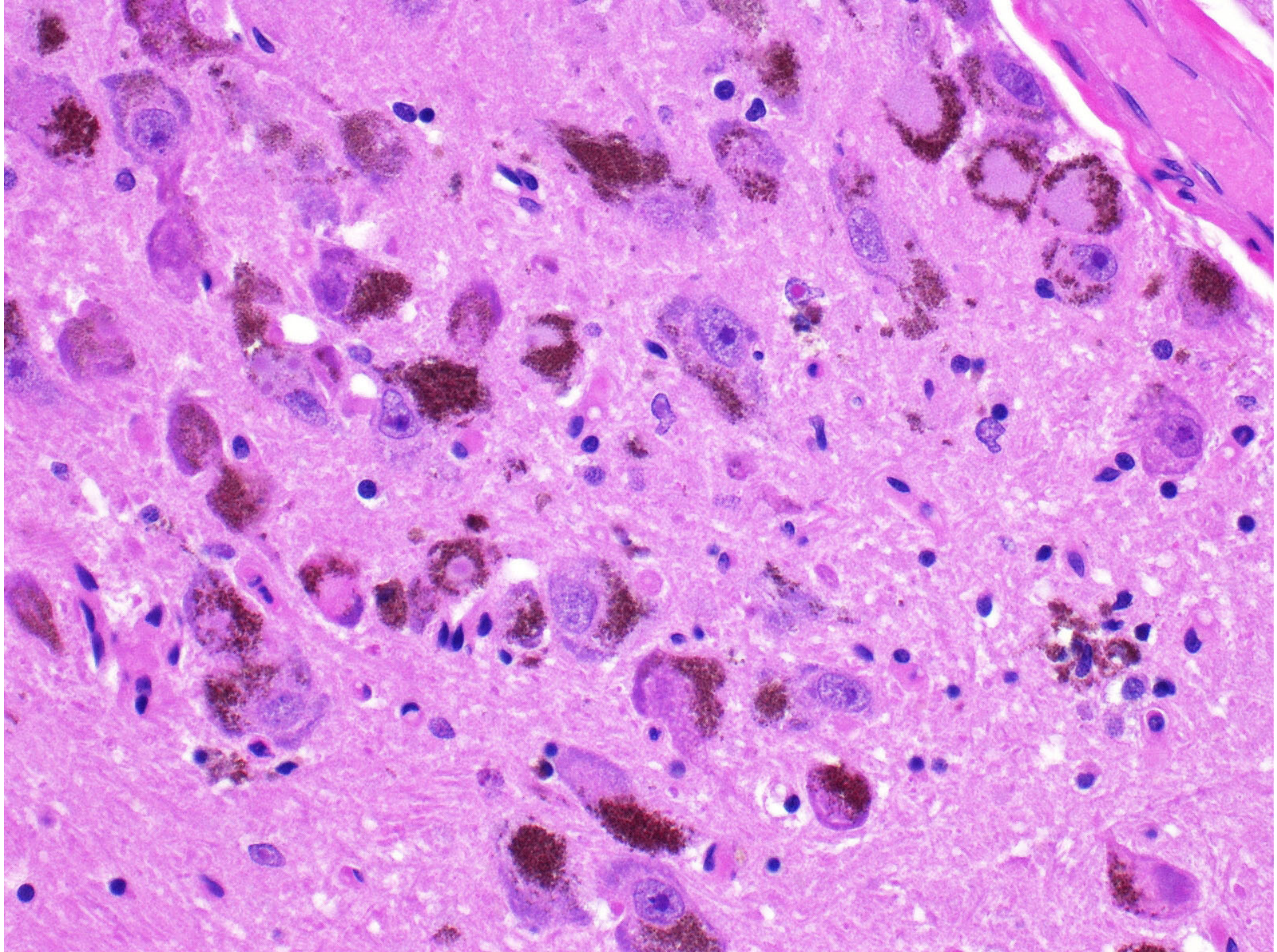



R

H&E, 40x
Nucleus Basalis

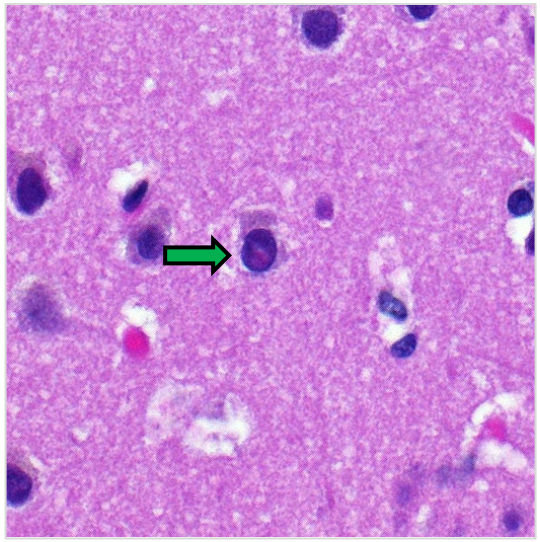


H&E, 40x
Substantia Nigra

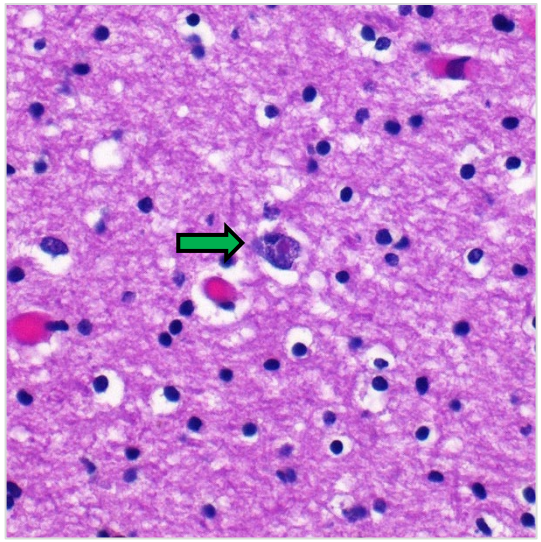


Diagnosis?

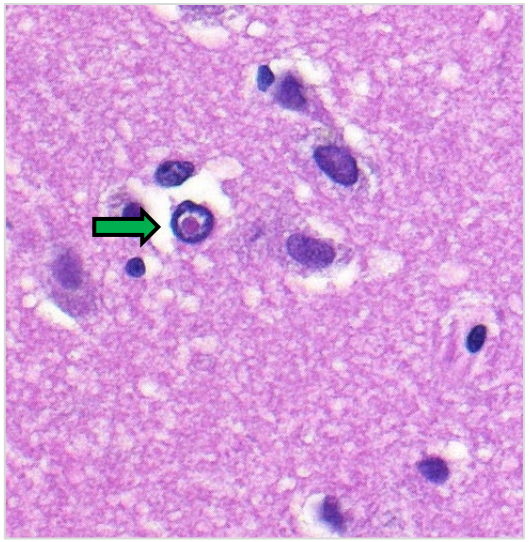
Frontal lobe



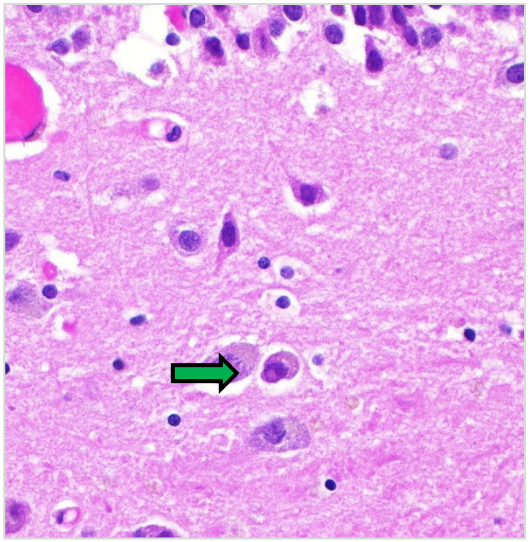
Temporal lobe



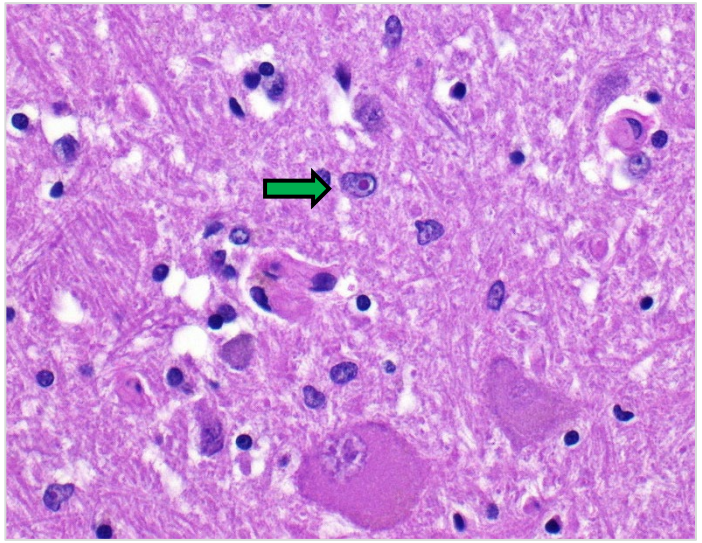
Amygdala

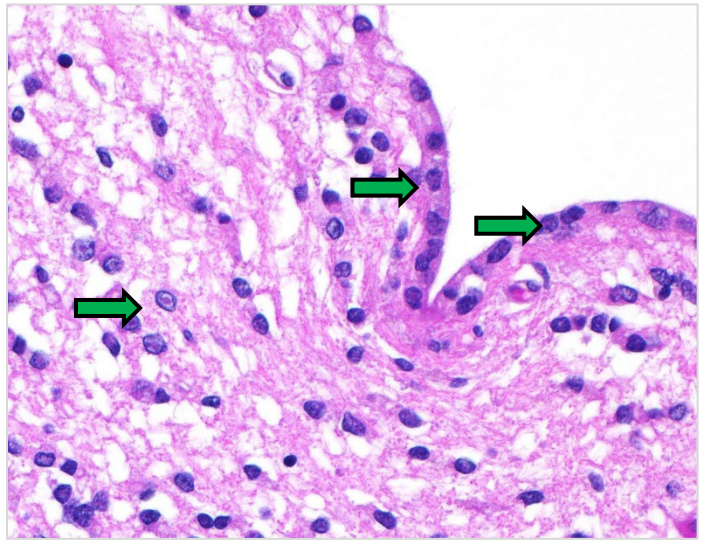


Hippocampus



Cervical cord

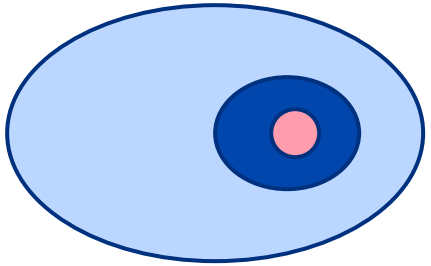




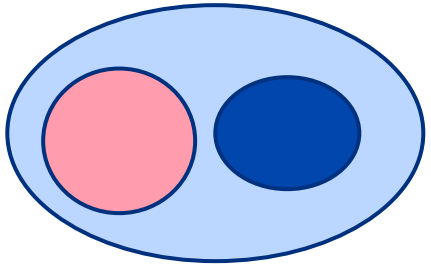
Ependyma, Basal ganglia

H&E, 40x

Differential Diagnosis – Spherical Inclusions



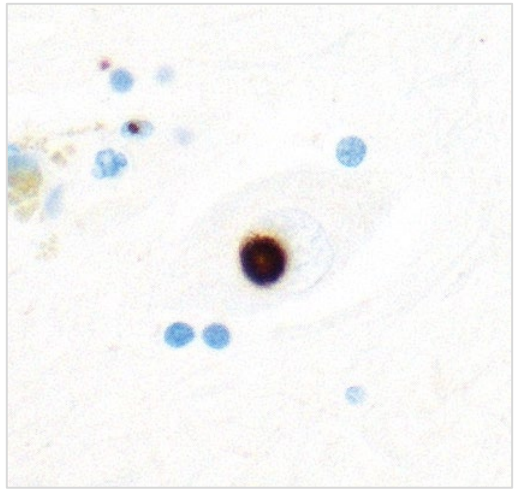
- FTLD-TDP-43 (Type D)
- FTLD-FUS (aFTLD-U)
- Neuronal intranuclear inclusion disease (NIID)
- Fragile X-associated tremor/ataxia syndrome (FXTAS)



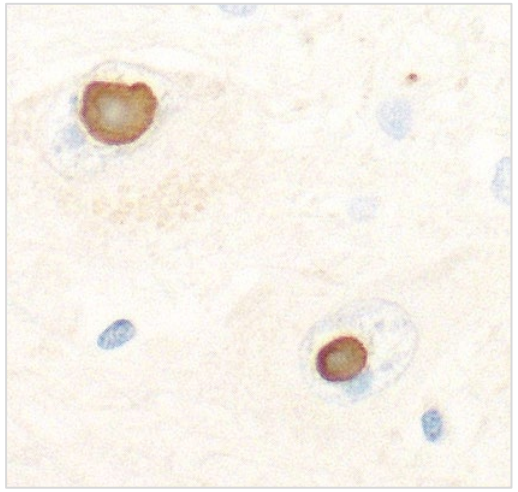
- Pick's disease
- FTLD-FUS - Basophilic inclusion body disease (BIBD)
- Atypical multiple system atrophy
- Lewy Body Disease

Amygdala, 40x

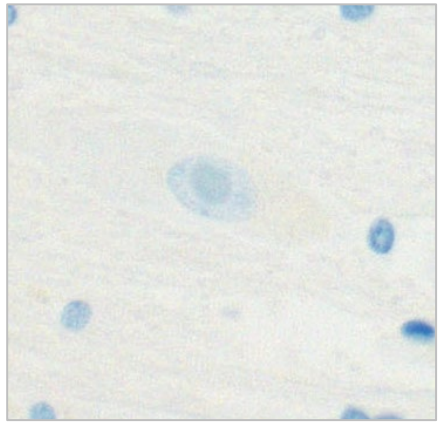
p62



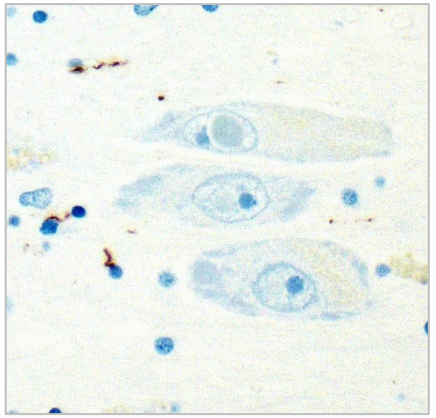
Ubiquitin



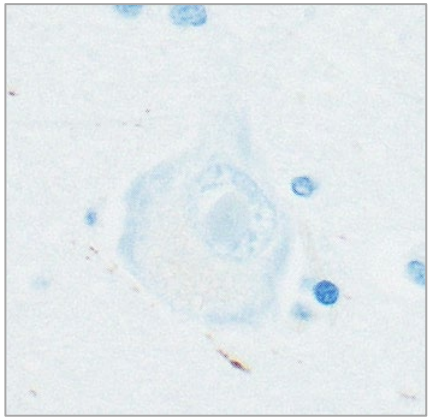
pTDP-43



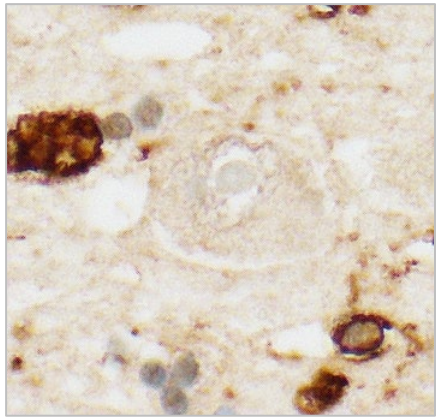
Alpha-synuclein



Tau

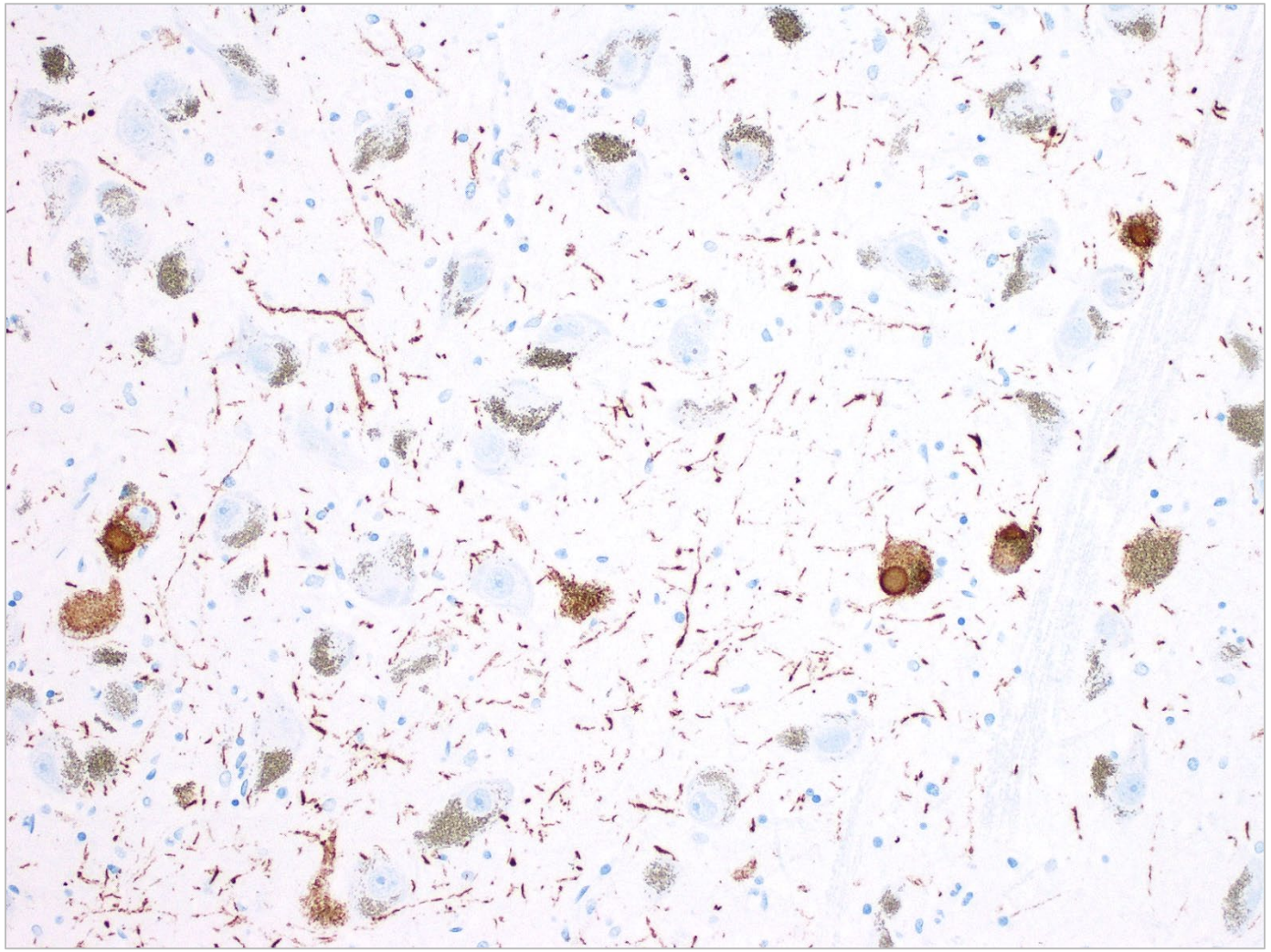


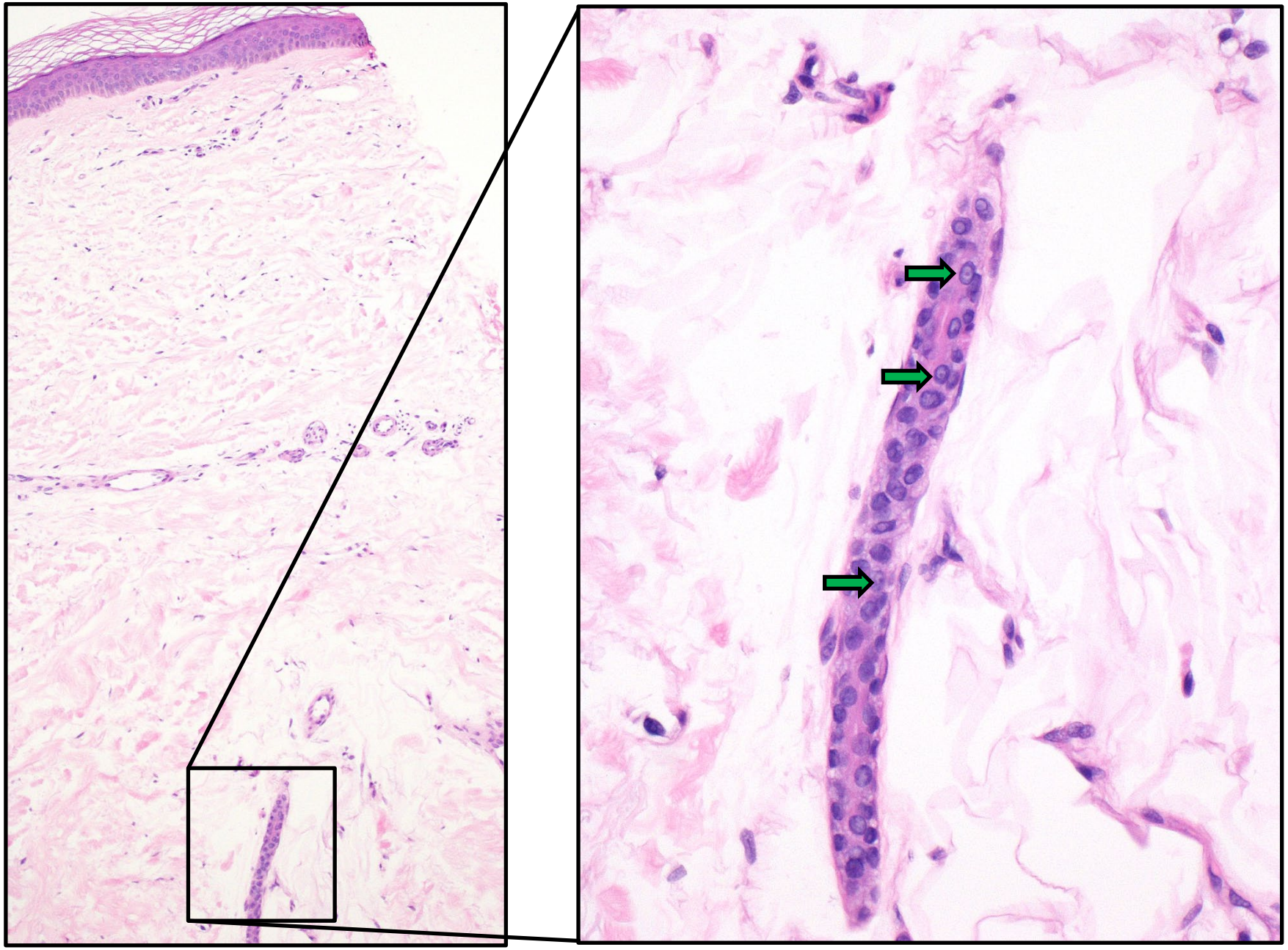
FUS

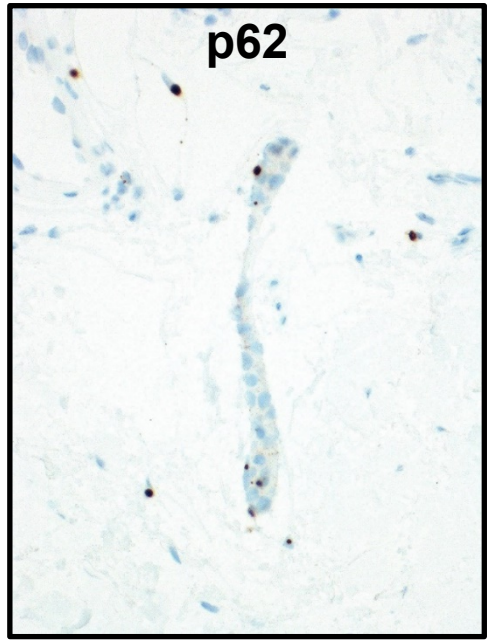


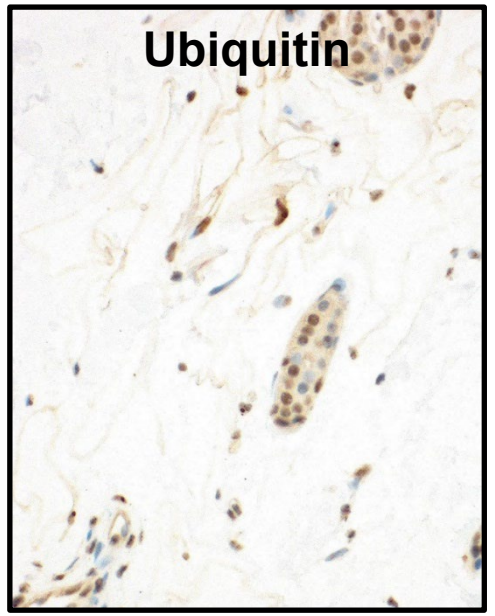
Substantia nigra, 20x

Alpha-synuclein

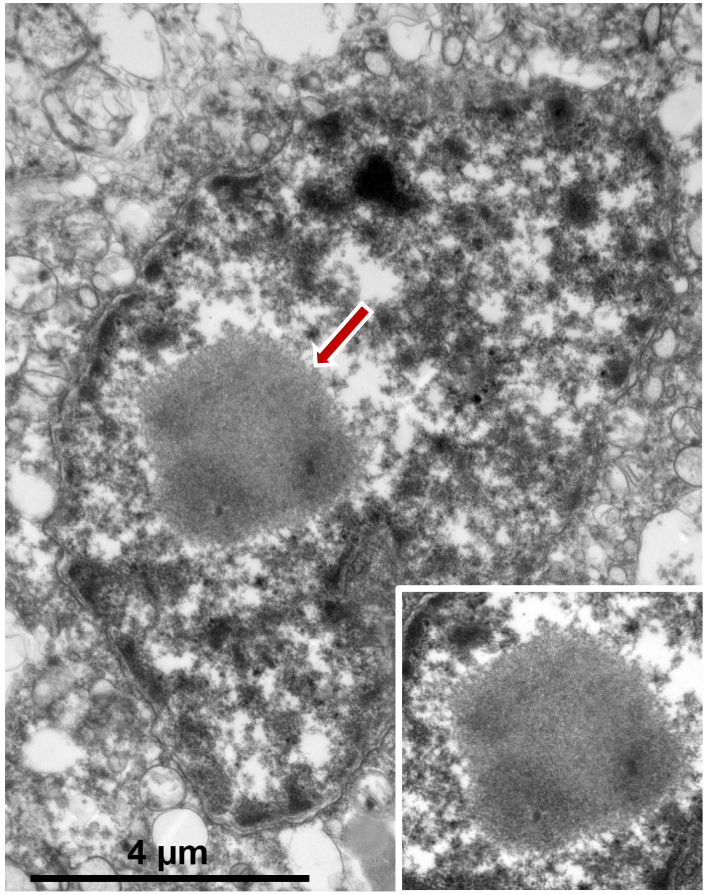


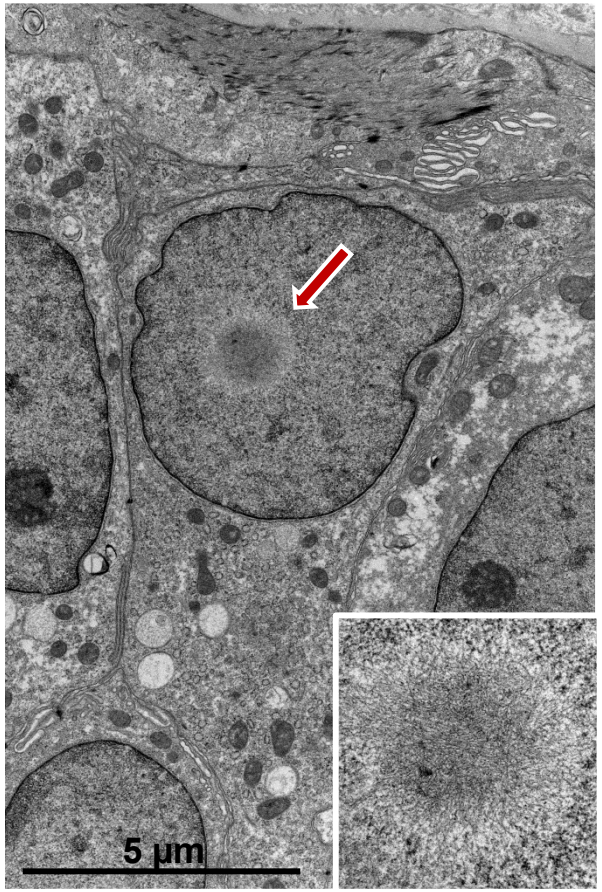



p62

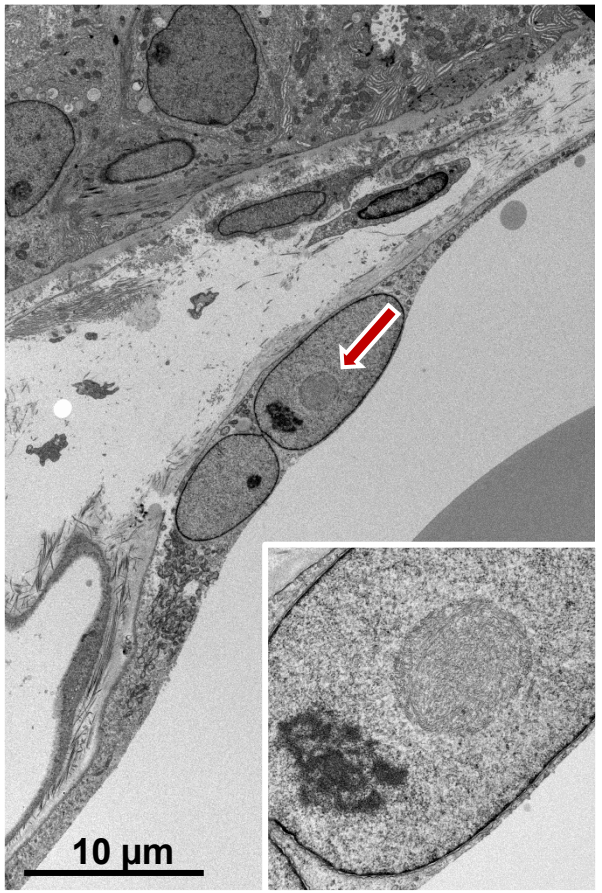

Ubiquitin

Nuclear Inclusions

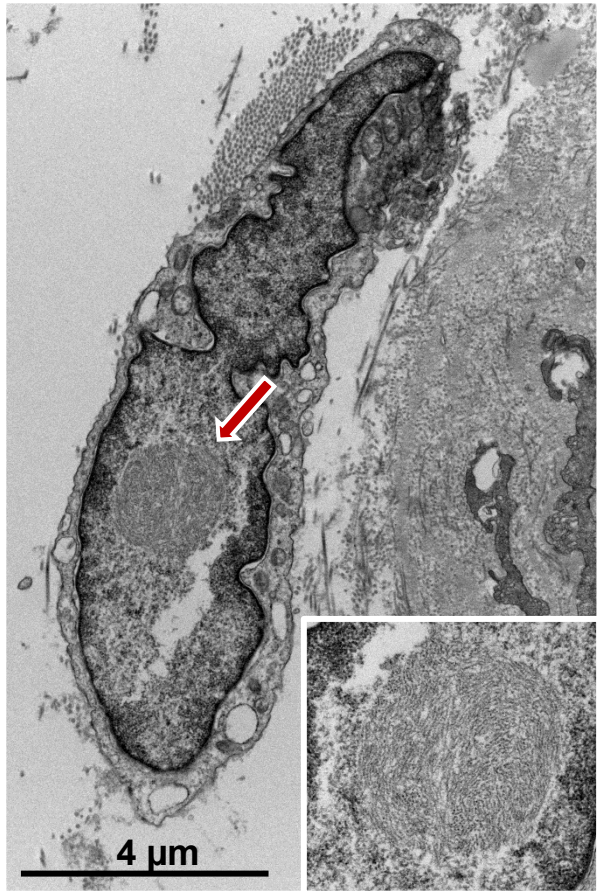




Glands

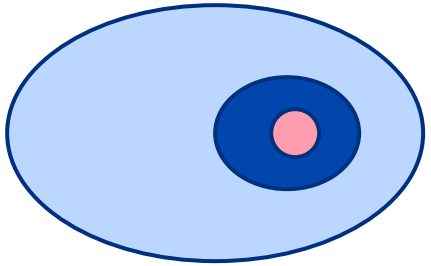


Endothelial cells

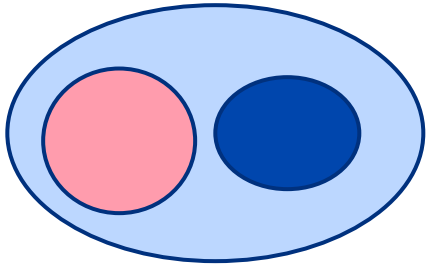


Fibroblasts

Revised Differential Diagnosis – Spherical Inclusions



- ~~FTLD-TDP-43 (Type D)~~
  - pTDP-43 -
- ~~FTLD-FUS (aFTLD-U)~~
  - Ubiquitin +, p62+, FUS -
- Neuronal intranuclear inclusion disease (NIID)
  - Ubiquitin+, p62+
- Fragile X-associated tremor/ataxia syndrome (FXTAS)
  - *FMR1* gene analysis



- Pick's disease
- [illegible]FUS
- Atypica[illegible]ystem
- L[illegible]ody D[illegible]e

Genetic Studies

- Mitochondrial DNA analysis negative
- Whole exome sequencing: *MACF1* variant unknown significance
- Fragile X syndrome was negative with a normal number of CGG repeats within the *FMR1* gene.

Final Diagnosis

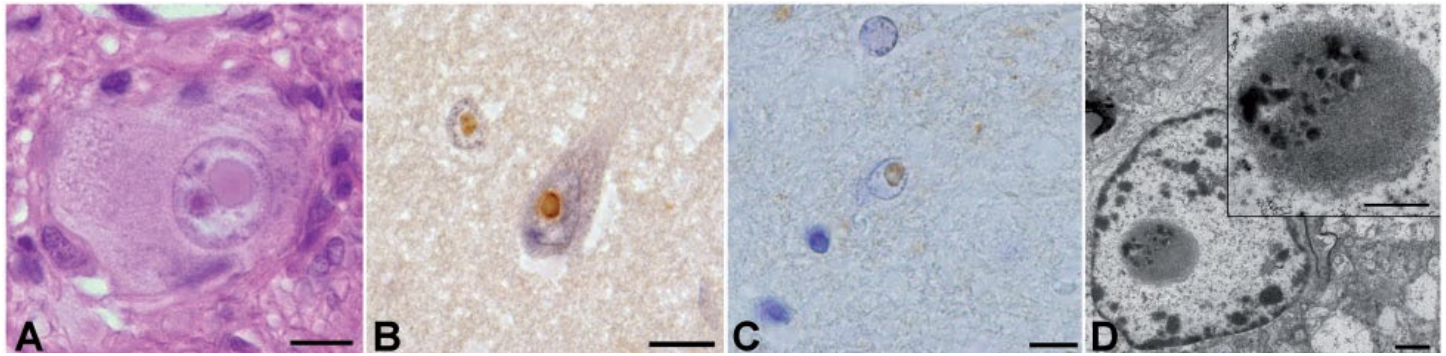
1. Neuronal intranuclear inclusion disease
2. Lewy body disease, limbic (transitional) type

Neuronal intranuclear inclusion disease (NIID)

- Slowly progressive neurodegenerative disease
- Onset varies from infancy to 6th decade
- Wide spectrum clinical presentation:
  - Pyramidal and extrapyramidal symptoms
  - Cerebellar ataxia
  - Dementia
  - Convulsions
  - Autonomic dysfunction
- Ante-mortem diagnosis difficult, previously sural and rectal biopsies performed
- Skin biopsy utility recently reported

NIID Histology

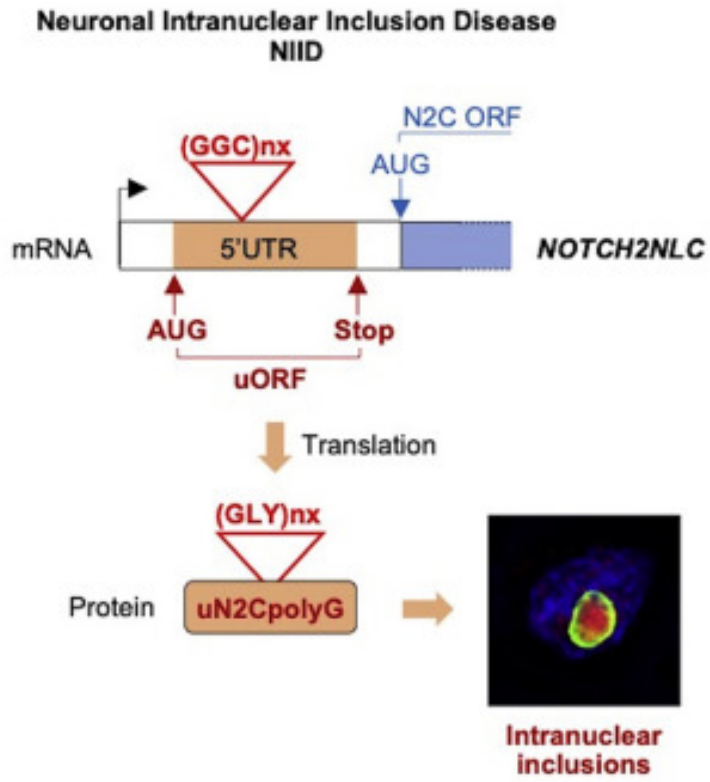
- Eosinophilic intranuclear inclusions involving central and peripheral nervous system, various organs including skin
- Ubiquitin and p62+, pTDP-43-
- Histopathological features resemble FXTAS:
  - No literature on skin biopsies
  - Genetic evaluation of *FMR1* premutation



Sone J, Mori K, Inagaki T, et al. Clinicopathological features of adult-onset neuronal intranuclear inclusion disease. *Brain*. 2016;139(12):3170-3186.

NIID Possible Toxic PolyG-protein Disorder

- Novel GC-rich microsatellite expansions recently reported in multiple disorders
  - FXTAS
  - NIID
  - Oculopharyngodistal myopathy (OPDM)
  - Oculopharyngeal myopathy with leukoenceophalopathy (OPML)
- NIID: Microsatellite expansion of GGC repeats in *NOTCH2NLC*



Boivin M, Deng J, Pfister V, et al. Translation of GGC repeat expansions into a toxic polyglycine protein in NIID defines a novel class of human genetic disorders: the polyG diseases. *Neuron*. 2021;0(0).

References

1. Love S, Perry A, Ironside J, Budka H, eds. *Greenfield's Neuropathology*. 9th edition. CRC Press; 2015.
2. Sone J, Mori K, Inagaki T, et al. Clinicopathological features of adult-onset neuronal intranuclear inclusion disease. *Brain*. 2016;139(12):3170-3186.
3. Sone J, Tanaka F, Koike H, et al. Skin biopsy is useful for the antemortem diagnosis of neuronal intranuclear inclusion disease. *Neurology*. 2011;76(16):1372-1376.
4. Sone J, Kitagawa N, Sugawara E, et al. Neuronal intranuclear inclusion disease cases with leukoencephalopathy diagnosed via skin biopsy. *Journal of Neurology, Neurosurgery & Psychiatry*. 2014;85(3):354-356.
5. Boivin M, Deng J, Pfister V, et al. Translation of GGC repeat expansions into a toxic polyglycine protein in NIID defines a novel class of human genetic disorders: the polyG diseases. *Neuron*. 2021;0(0).

Thank you!

Questions?

Summarized Discussion Points

- Differential diagnosis for nuclear spherical inclusions:
  - FTLD-TDP-43 (type D)
  - FTLD-FUS (aFTLD-U)
  - Neuronal intranuclear inclusion disease (NIID)
  - Fragile X-associated tremor/ataxia syndrome (FXTAS)
- Neuronal Intranuclear Inclusion Disease (NIID):
  - Neurodegenerative disorder with broad spectrum of clinical presentation
  - Histologically characterized by eosinophilic, nuclear inclusions which are p62/ubiquitin+, while negative for FUS and pTDP-43
- Useful ante-mortem tests:
  - Rectal and sural nerve biopsy (higher morbidity)
  - Skin biopsy
  - *FMR1* premutation analysis
- NIID may represent toxic poly-G protein disorder

