

# 2015 AANP: Diagnostic Slide Session

## Case 6

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# Disclosures

No relevant financial  
relationships or conflicts  
of interest

# Clinical History

- A 35-year-old African-American man
- 5 years of slowly progressive gait disturbance and dysarthria
- HIV , poor adherence to antiretroviral medications (CD4+ nadir of 16)
- In his 20s - a boxer, had sustained a total of 3 knockouts
- No family history of neurologic disease

## **Neurologic examination at presentation**

- Normal mental status
- Gait - wide-based, unsteady
- Dysarthria, decreased facial expression, slow saccades, mild impairment of upward gaze
- Mild symmetric lower extremity weakness (distal and proximal), spasticity
- Mildly reduced vibratory sense in the toes

**Progressive neurologic course:** nystagmus, dysmetric saccades, ataxia, spasticity involving UE, worsening dysarthria and hypophonia, peripheral neuropathy

- MRI of the brain: a mild, diffuse cerebral and cerebellar atrophy, more marked brainstem atrophy.

A diagnostic molecular test was performed

At the time of death (50yo) - bed bound, tracheostomy, communicates via blinking his eyes.

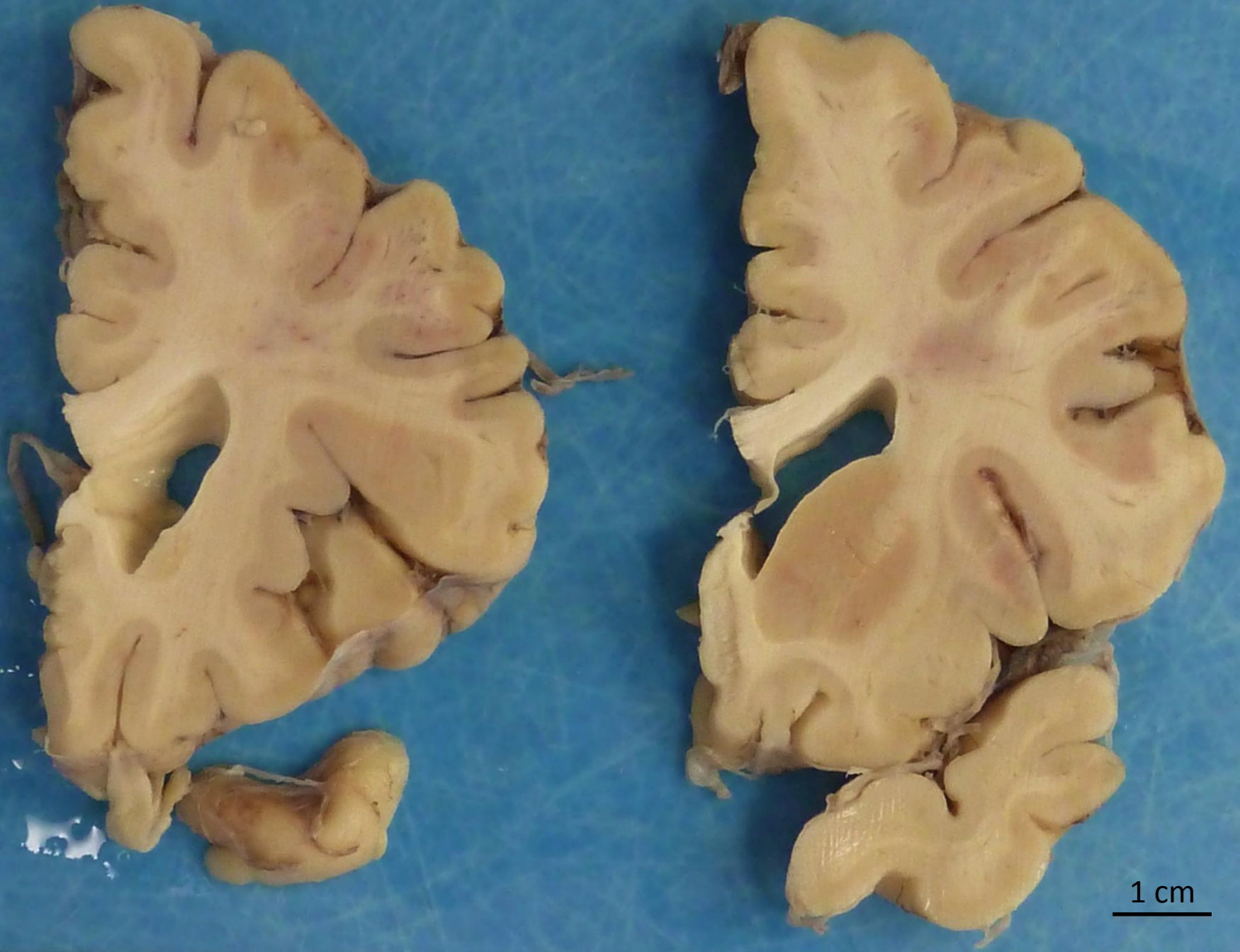
Brain 1150 g



010072

1 cm





1 cm

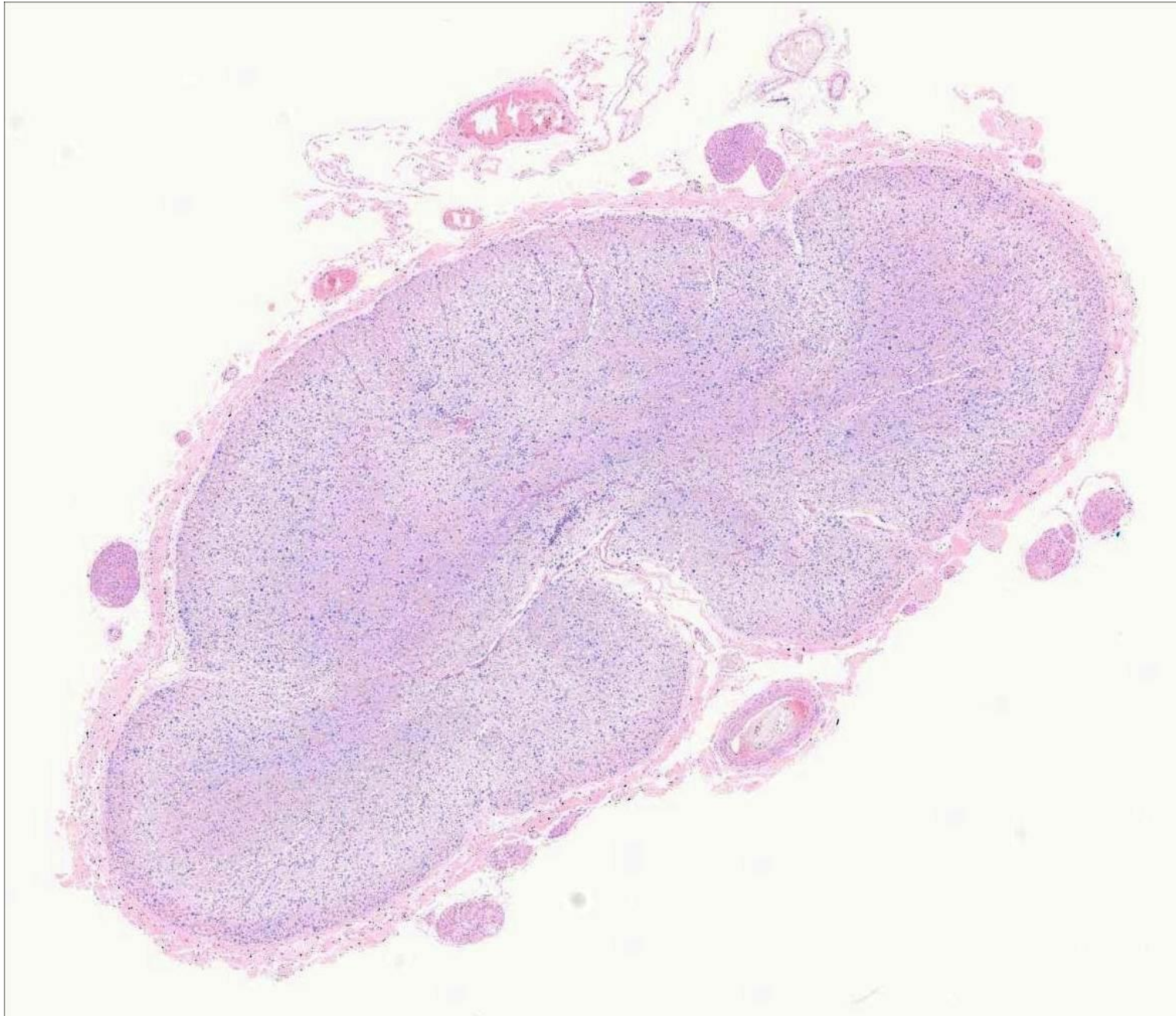
# Cerebellum and pons

1 cm





# Spinal cord

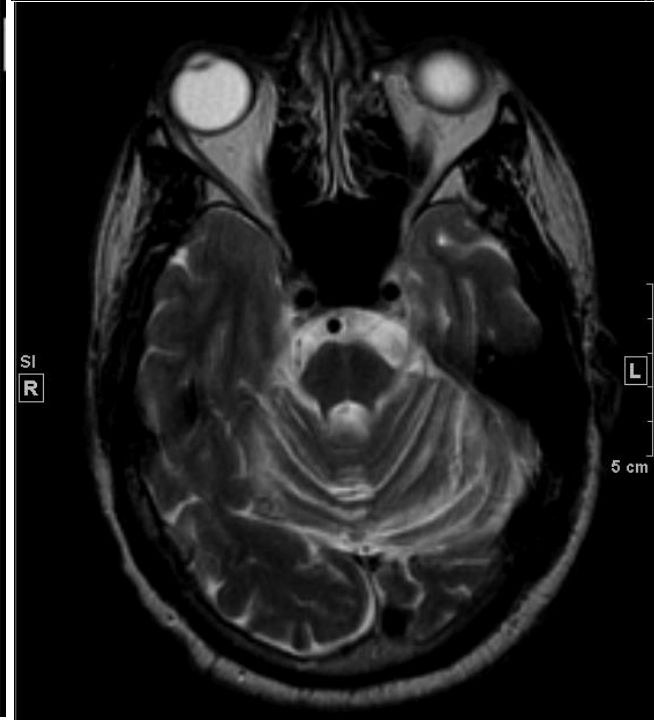


1. What was the diagnostic molecular test?

2. What is the diagnosis?

3. Is the neuropathology typical of this disorder?





# Diagnostic molecular test

Testing for the CAG repeat expansion (Ataxia profile) was performed at **Athena Diagnostics, Inc.**

- SCA1 allele 1: 30 CAG repeats (N:  $\leq 34$ )
- SCA1 allele 2: 30 CAG repeats
- SCA2 allele 1: 23 CAG repeats (N:  $\leq 31$ )
- SCA2 allele 2: 23 CAG repeats
- **MJD (SCA3) allele 1: 72 CAG repeats** (N:  $\leq 40$ , B: 41-60)
- **MJD (SCA3) allele 2: 38 CAG repeats**
- SCA6 allele 1: 13 CAG repeats (N:  $\leq 18$ )
- SCA6 allele 2: 11 CAG repeats
- SCA7 allele 1: 10 CAG repeats (N:  $\leq 18$ )
- SCA7 allele 2: 10 CAG repeats

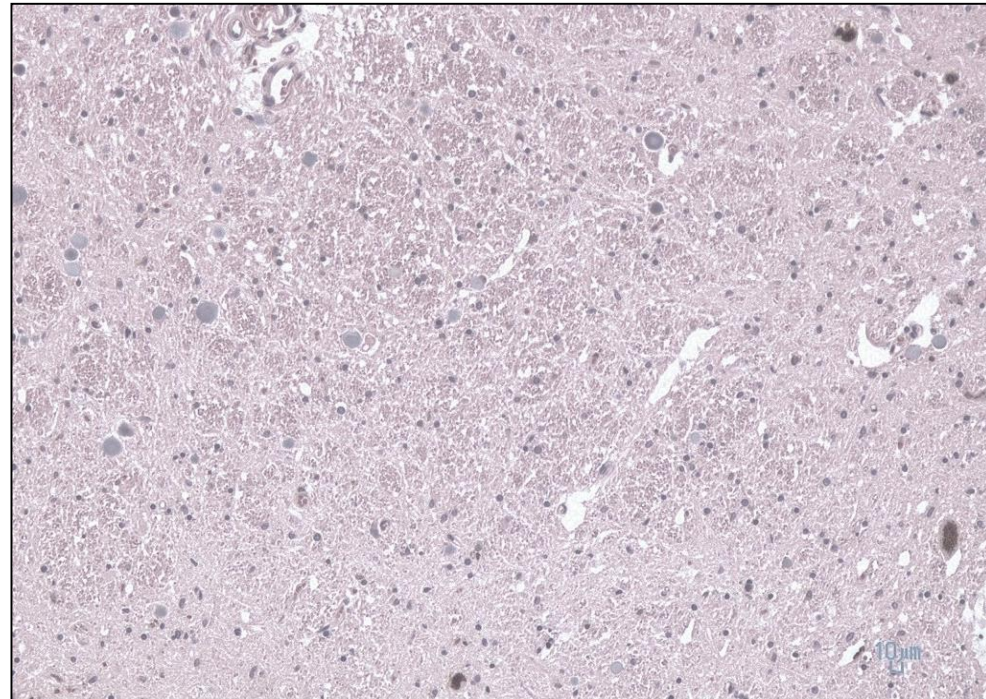
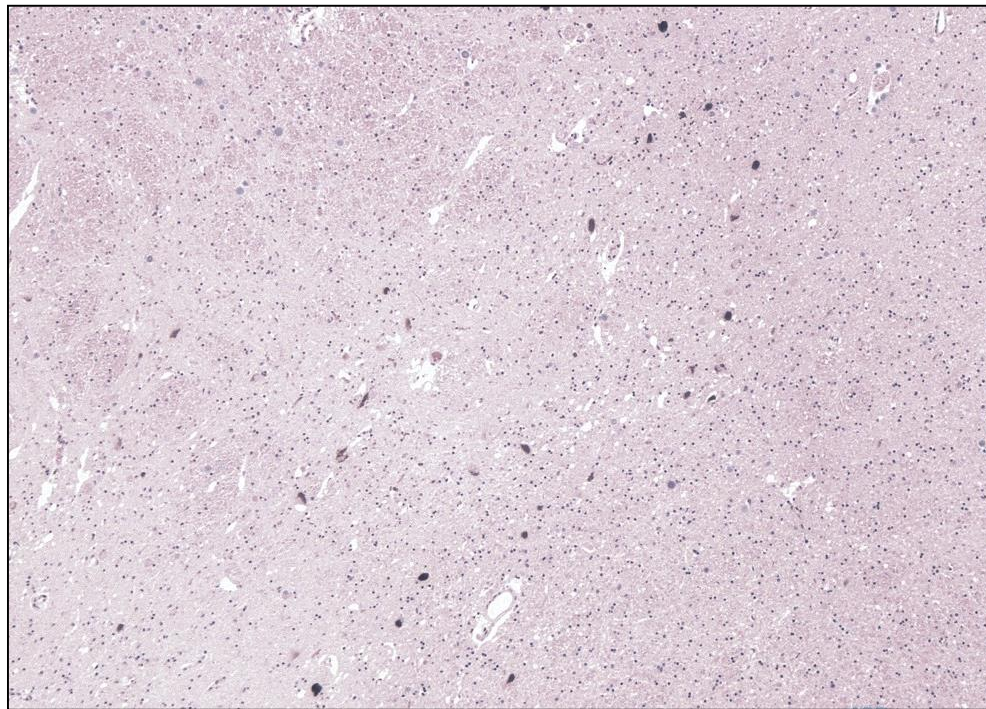
# Neuropathology Findings



# Midbrain with s. nigra



1 cm





# Pons, LFB

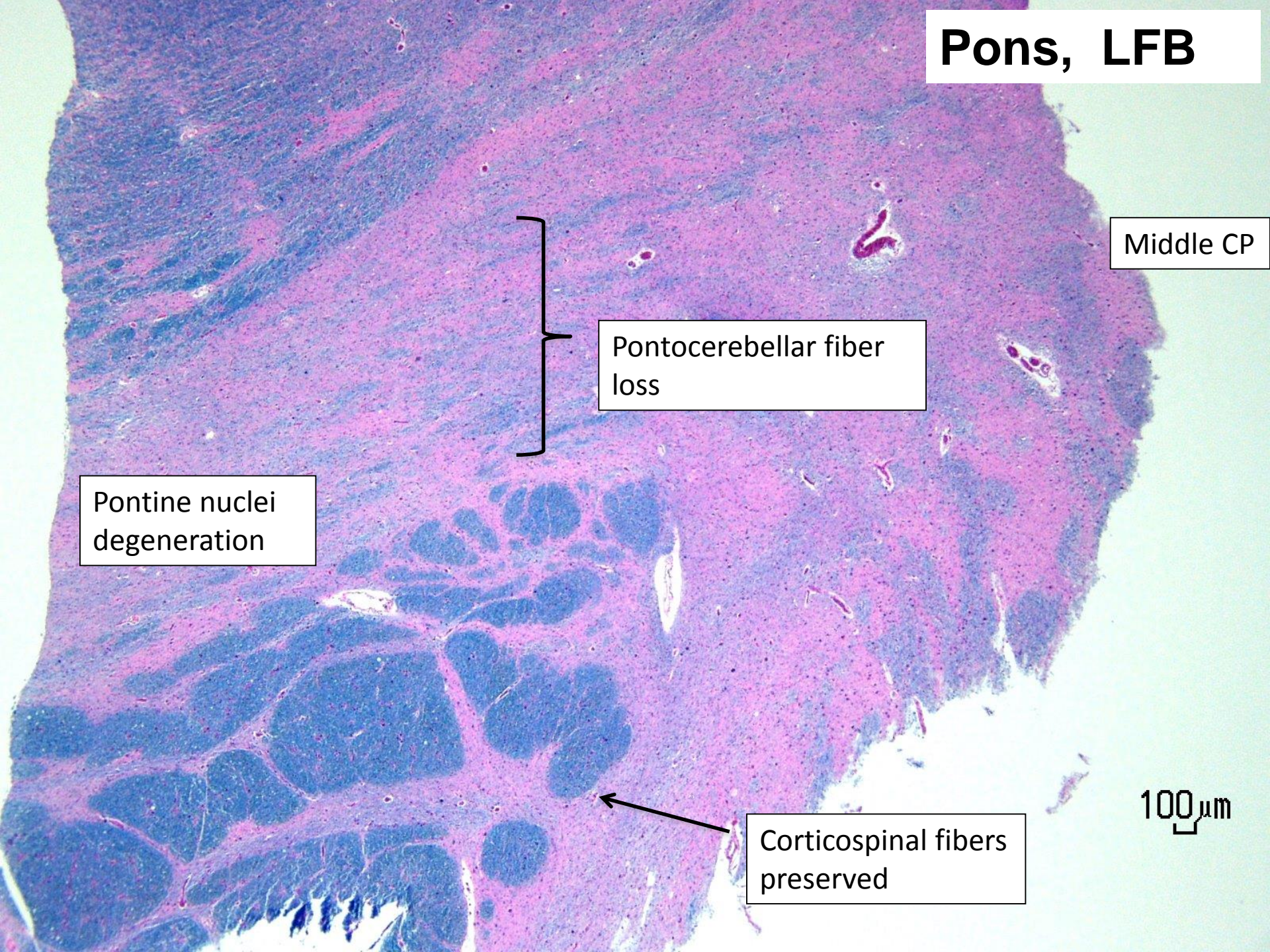
Middle CP

Pontocerebellar fiber  
loss

Pontine nuclei  
degeneration

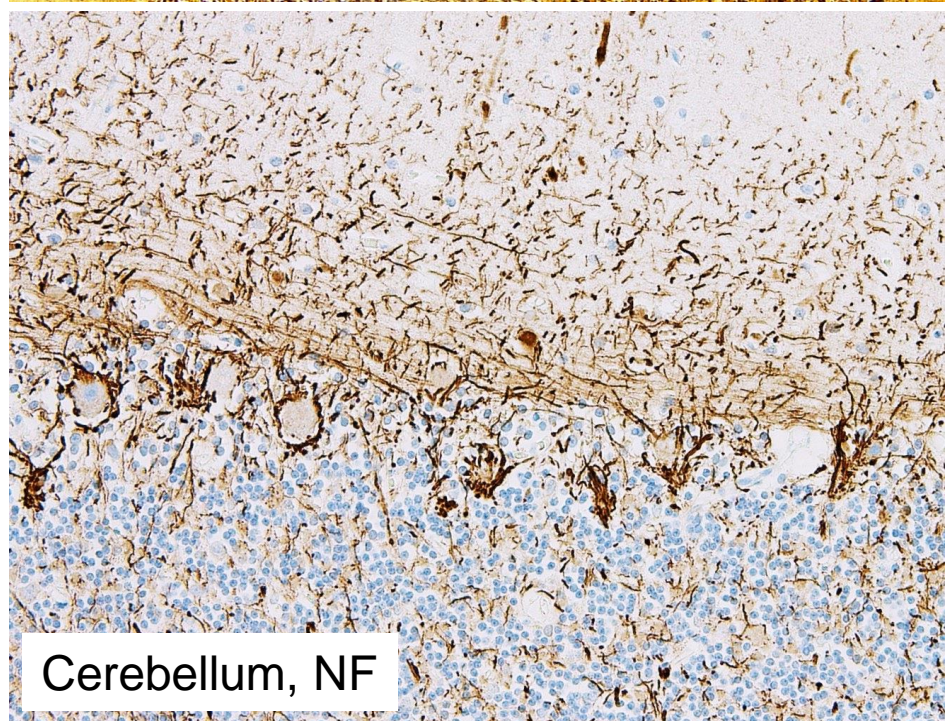
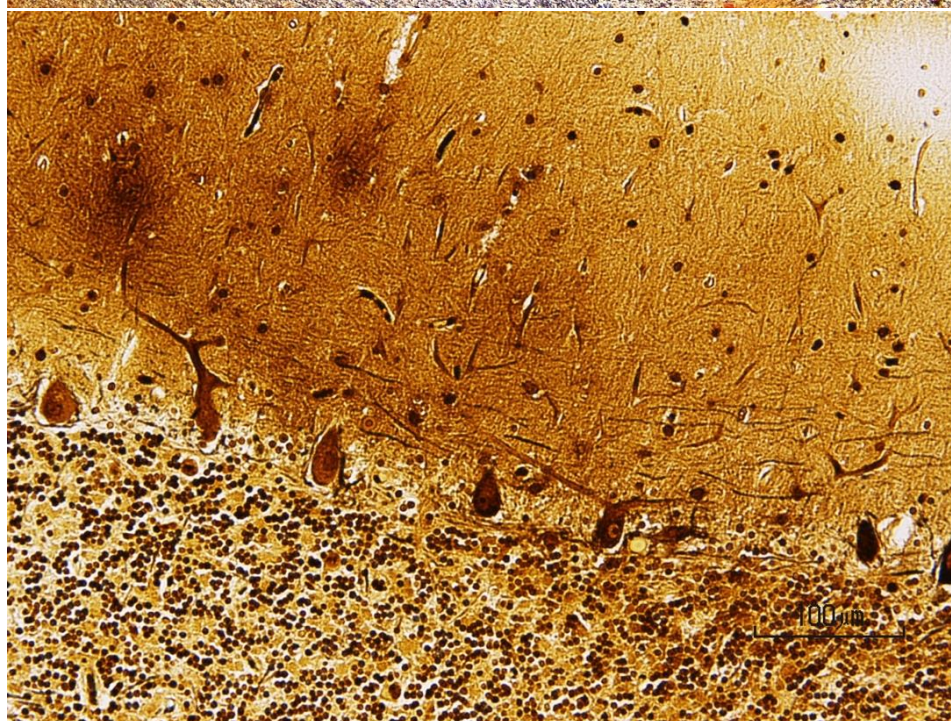
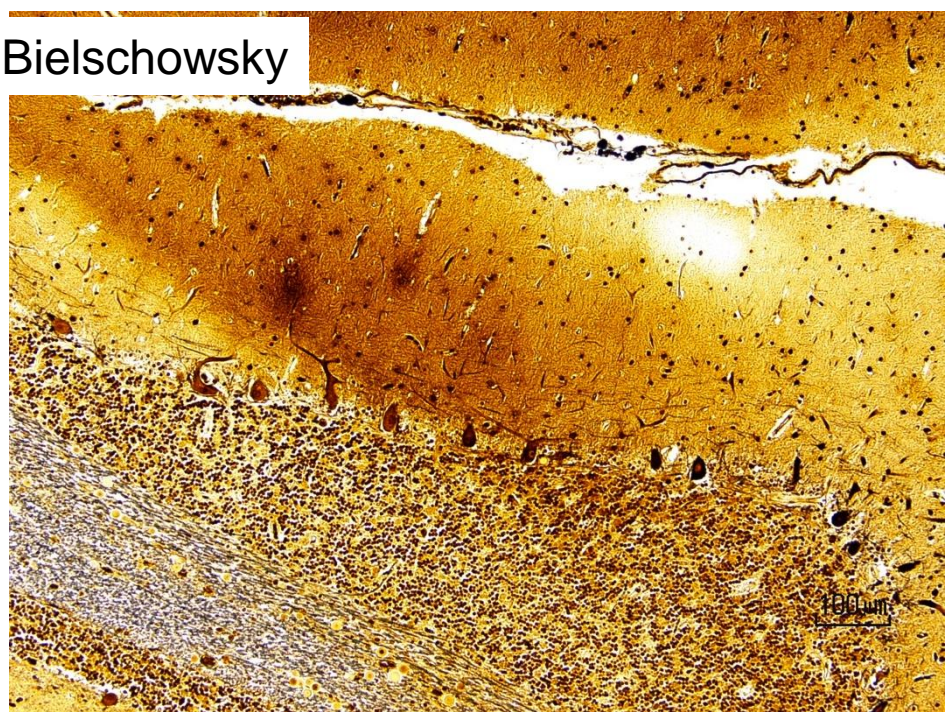
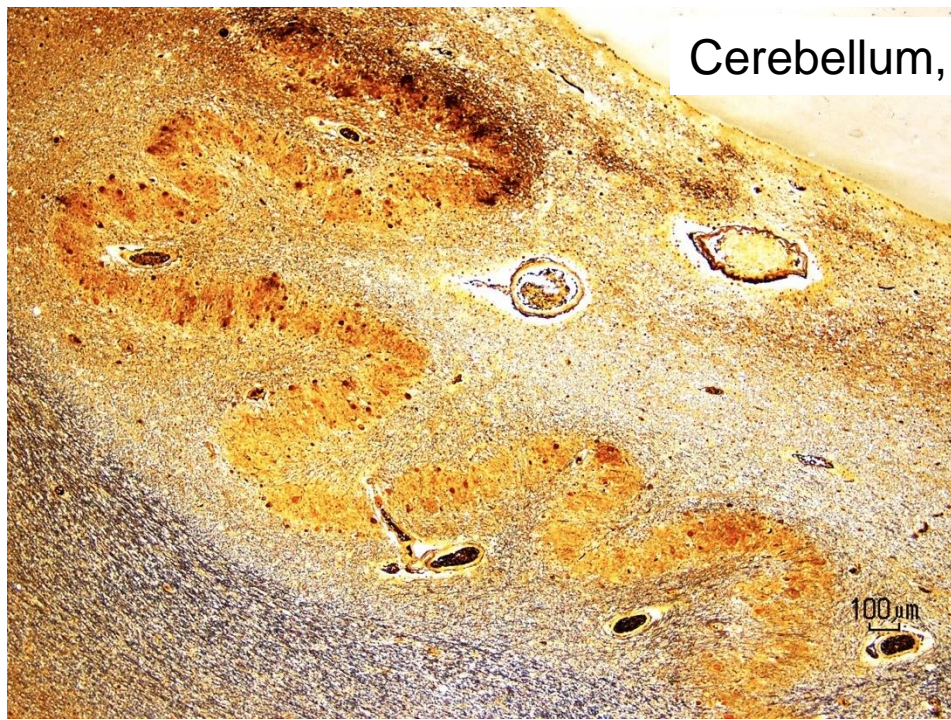
Corticospinal fibers  
preserved

100  $\mu$ m



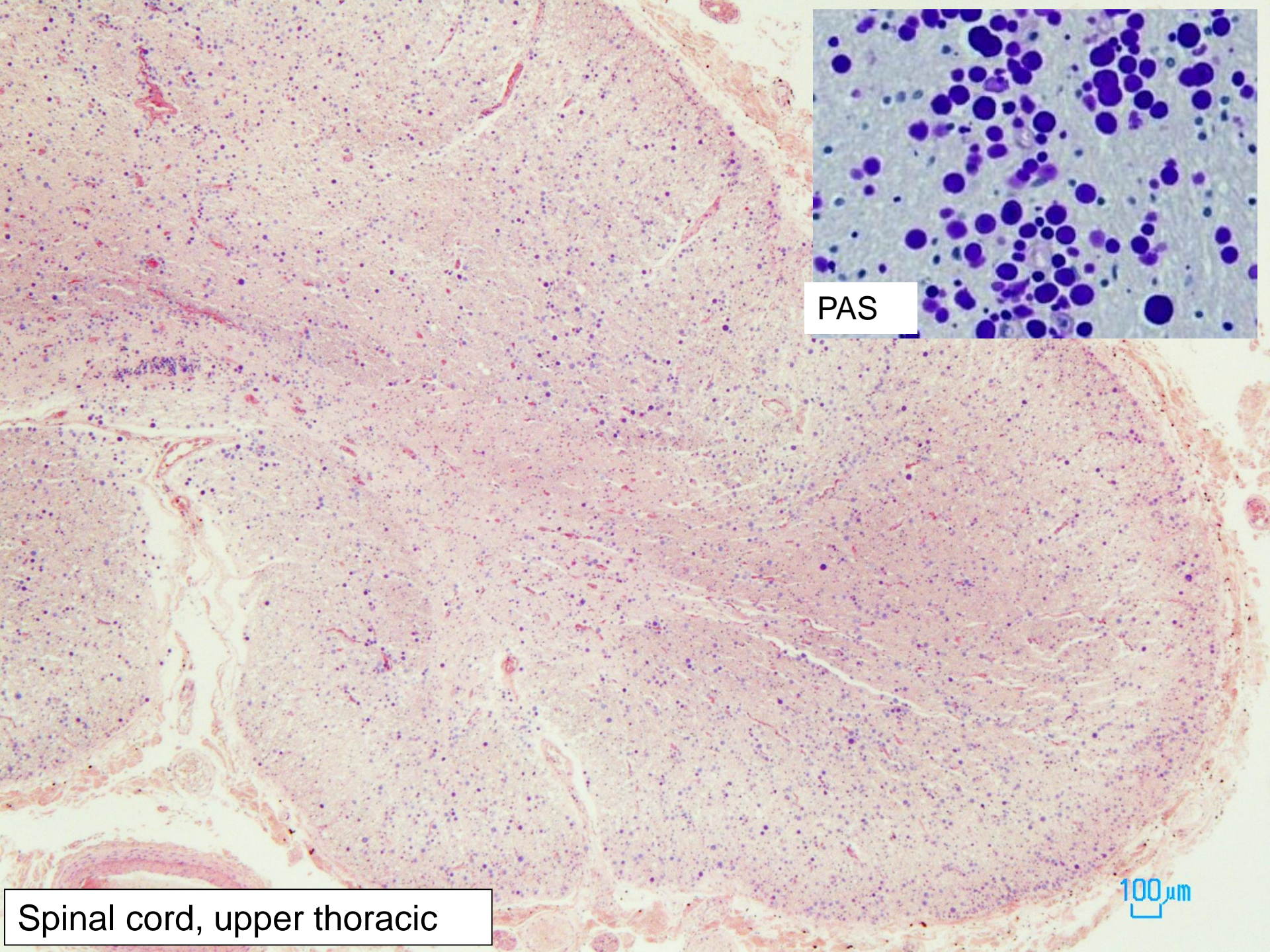


Cerebellum, Bielschowsky



Cerebellum, NF





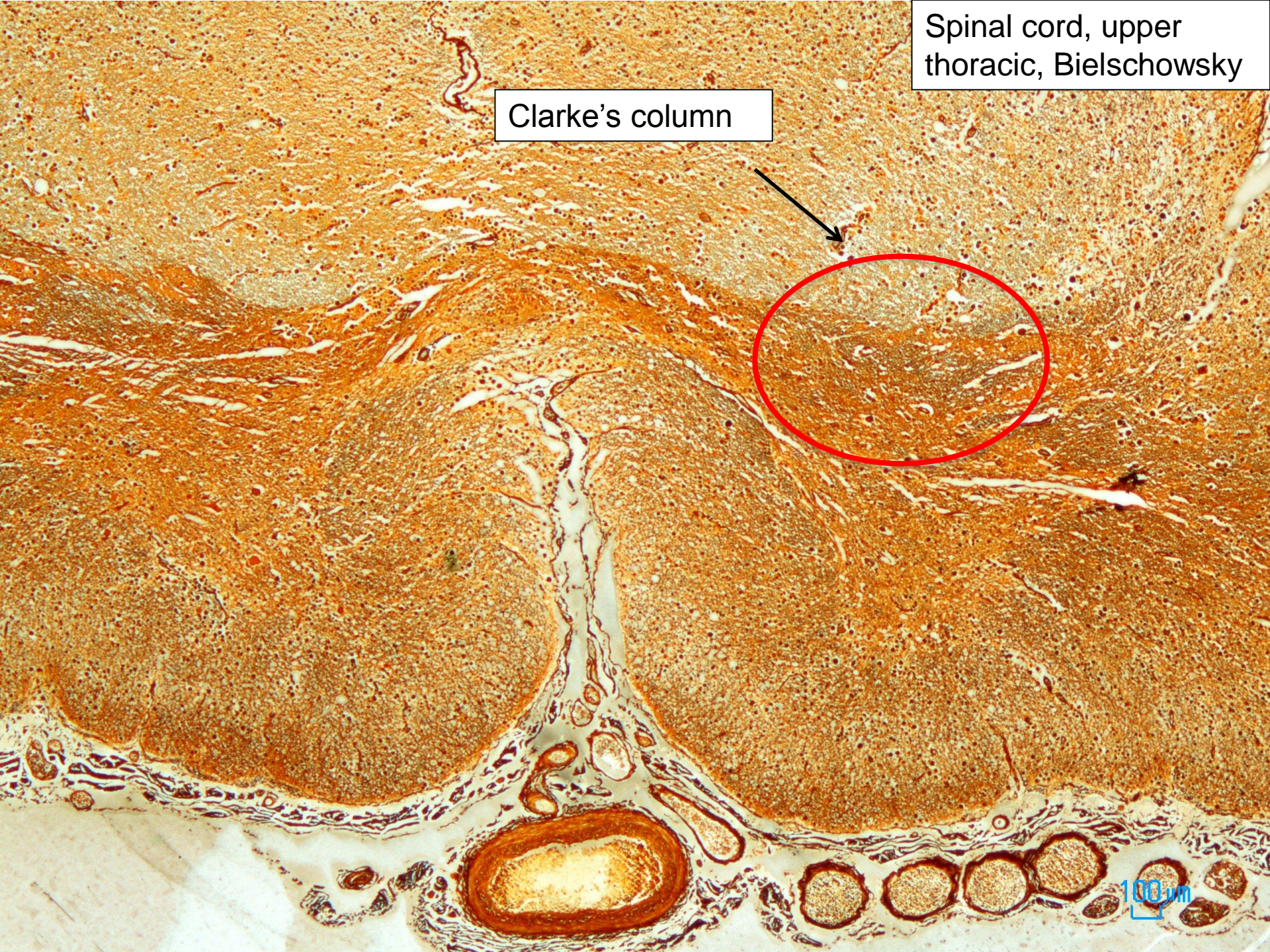
PAS

100 μm

Spinal cord, upper thoracic



Clarke's column



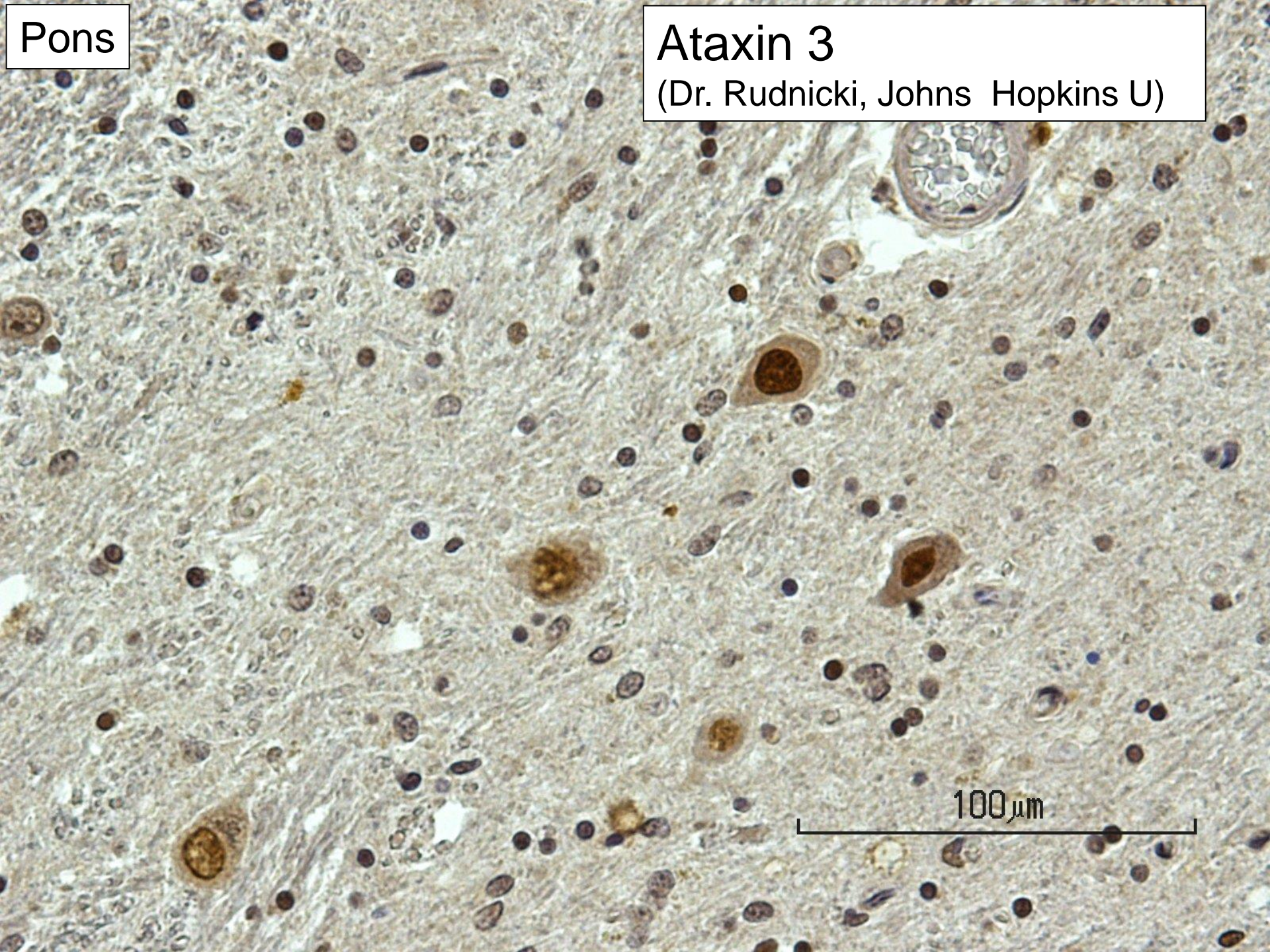
100 μm



Pons

Ataxin 3

(Dr. Rudnicki, Johns Hopkins U)



100 μm



# Diagnosis

Spinocerebellar ataxia type 3 (SCA3)/  
Machado-Joseph disease (MJD)

with

numerous polyglucosan bodies in HIV+  
African-American male with history of  
head trauma

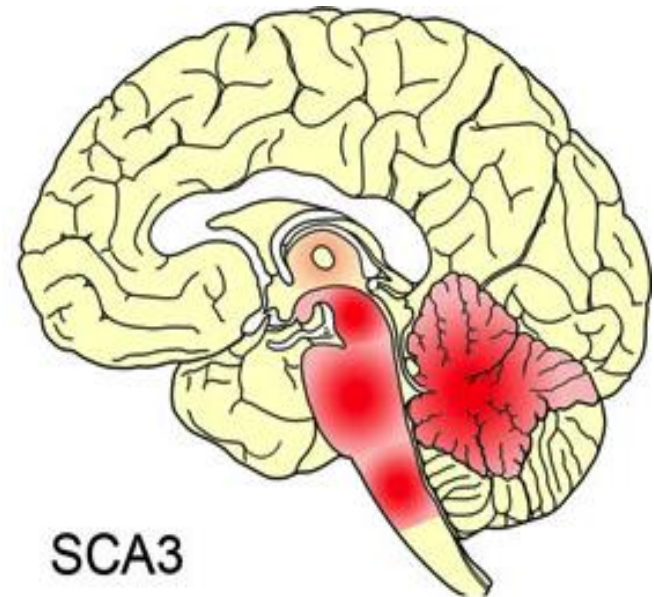
# Hereditary ataxias

updated list - <http://neuromuscular.wustl.edu/ataxia/recatax.html>

AD	AR	X-link	Mit
<p><b>1. SCA 1-41</b> Repeat expansion, &gt; CAG, mutations</p> <ul style="list-style-type: none"> <li>Cerebellar cortical atrophy,</li> <li>OPCA</li> <li>Spinocerebellar degeneration</li> </ul> <p><b>2. DRPLA</b> CAG expansion in atrophin-1 (12p) - 49-75 (n – 7-23)</p> <ul style="list-style-type: none"> <li>Chorea, myoclonic epi, dementia (simul of HD)</li> <li>Neuronal loss: DN, GP, subthalamic, caudate, putamen, SN, inf olives</li> <li>Atrophy of sup CP</li> <li>Degeneration of post spinal columns and spinocerebellar tracts</li> </ul> <p><b>3. Episodic ataxias EA1-8</b> <b>4. Dominant ataxia s-mes</b></p>	<p><b>1. Friedreich ataxia</b> 9q <i>FRDA</i> – frataxin: 95% - GAA 500-1000 (n- 6-34) Degeneration:</p> <ul style="list-style-type: none"> <li>Spinal cord - post columns, distal spino-cerebellar and pyramidal tracts, Clarke's</li> <li>DRG, large myelin axons from post roots</li> <li>Medulla: accessory cuneate and gracile n., sup. olives</li> <li>2* ischemic changes (cardiomyopathy)</li> </ul> <p><b>2. Ataxia w vit E def</b> α-tocopherol transfer protein, similar to FA</p> <p><b>3. Mitochondrial recessive ataxia s-me</b> Mut POLG – DNA-polymerase-γ: depletion of mt DNA in PN and skeletal muscle:</p> <ol style="list-style-type: none"> <li>SCAE – cerebellar and sensory</li> <li>SANDO – sensory ataxia w. periph neuropathy, dysarthria and ophthalmoplegia</li> </ol> <p><b>4. DNA repair s-mes (AT, XP, Cockayne ERCC, MRE11A)</b> <b>5. SCAR 1-20</b></p>	<p><b>1. FXTAS</b> CGG expansion in 5' UTR of FMR1 - 55-200 – premutation</p> <ul style="list-style-type: none"> <li>Cortical atrophy</li> <li>Loss of Purkinje cells,</li> <li>Axon and myelin loss in wm</li> <li>Intranucl inclusions (N, A)</li> </ul> <p><b>2. SCAX 1-5</b></p> <p><b>3. Congenital and recessive diseases with cerebellar aplasia</b></p>	<p><b>1. MERFF</b> tRNA (lys, leu)</p> <p><b>2. MELAS</b> tRNA leu</p> <p><b>3. NARP</b> ATPase 6 gene</p>

# Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD)

- The most frequent subtype of AD SCA. Originated from founders in the Iberia Peninsula, who migrated to the Azores
- CAG repeat expansion > 55 units in the *ATXN3* gene, 14q32.1 region
- Intranuclear aggregates of ataxin-3, proteasome subunits and transcription factors (TBP and CBP)
- The clinical variability: length of repeats and the age at onset
- Anticipation of the phenotype: most frequently a/w paternal transmission
- Neuronal loss in midbrain, pons, medulla oblongata, cerebellum, Clarke's columns, +/- BG, thalamus, cerebral cortex



Seidel et al. Acta Neuropathol. 2012 Jul;124(1):1-21.

# Why are so many corpora amylacea?

## Has this been described before?

FL

100  $\mu$ m

Hip

100  $\mu$ m

- Adult polyglucosan body disease: AR or sporadic a/w the diffuse accumulation of abnormally branched glycogen in polyglucosan bodies.
- 5<sup>th</sup> – 7<sup>th</sup> decades: neurogenic bladder and motor neuron dysfunction, +/- dementia, peripheral neuropathy and cerebellar dysfunction
- Familial APBD due to mutations in the **Glycogen branching enzyme gene (*GBE1*, 3p12.2)**
- Mutations in *GBE1* are also causative of Glycogen Storage Disease type IV (GSDIV) - usually infantile liver disease or skeletal/cardiac myopathy

**Nucleotide variations in case #6:** T507A, Y114Y, two additional nucleotide variations in introns



## Case reports:

- Felice KJ et al. Childhood-onset spinocerebellar syndrome associated with massive polyglucosan body deposition. *Acta Neurol Scand.* 1997 Jan;95(1):60-4.
- Urkasemsin G et al. Mapping of Purkinje neuron loss and polyglucosan body accumulation in hereditary cerebellar degeneration in Scottish terriers. *Vet Pathol.* 2012 Sep;49(5):852-9



# Thank You !

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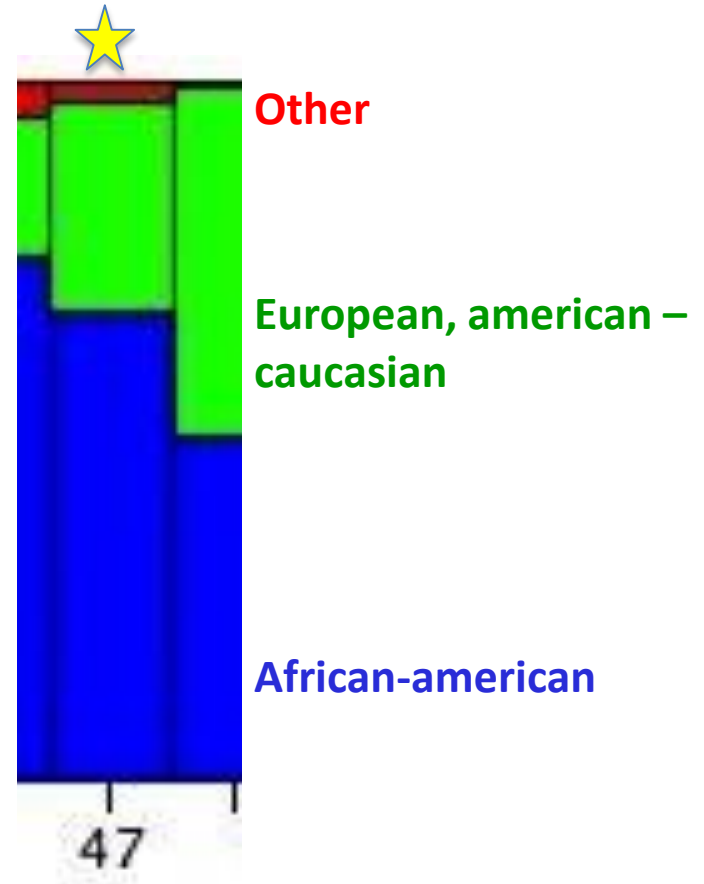
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1. Durr A et al. Spinocerebellar ataxia 3 and Machado-Joseph disease: clinical, molecular and neuropathological features. *Ann Neurol*. 1996;39:490–499.
2. Felice KJ et al. Childhood-onset spinocerebellar syndrome associated with massive polyglucosan body deposition. *Acta Neurol Scand*. 1997 Jan;95(1):60-4.
3. Loesch D, Hagerman R. Unstable mutations in the FMR1 gene and the phenotypes. *Adv Exp Med Biol*. 2012; 769:78-114.
4. Paulson H. Machado-Joseph disease/spinocerebellar ataxia type 3. *Handb Clin Neurol*. 2012;103:437-49.
5. Seidel et al. Brain pathology of spinocerebellar ataxias. *Acta Neuropathol*. 2012 Jul;124(1):1-21.
6. Takiyama Y et al. Evidence for intergenerational instability in the CAG repeat in the MJD1 gene and for conserved haplotypes at flanking markers amongst Japanese and Caucasian subjects with Machado-Joseph disease. *Hum Mol Genet*. 1995;4:1137–1146.
7. Urkasemsin et al. Mapping of Purkinje neuron loss and polyglucosan body accumulation in hereditary cerebellar degeneration in Scottish terriers. *Vet Pathol*. 2012 Sep;49(5):852-9

# Q1. Why does an African-American has a disease typically associated with the Portuguese ancestry?

## Two main ancestral haplotypes in MJD:

1. The Machado lineage, predominant in families of **Portuguese** extraction
2. The Joseph lineage, which is much older and worldwide spread, postulated to have an **Asian** origin.



Patient's (ID – 47) ancestry markers:  
~76% African American,  
~24% European American