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

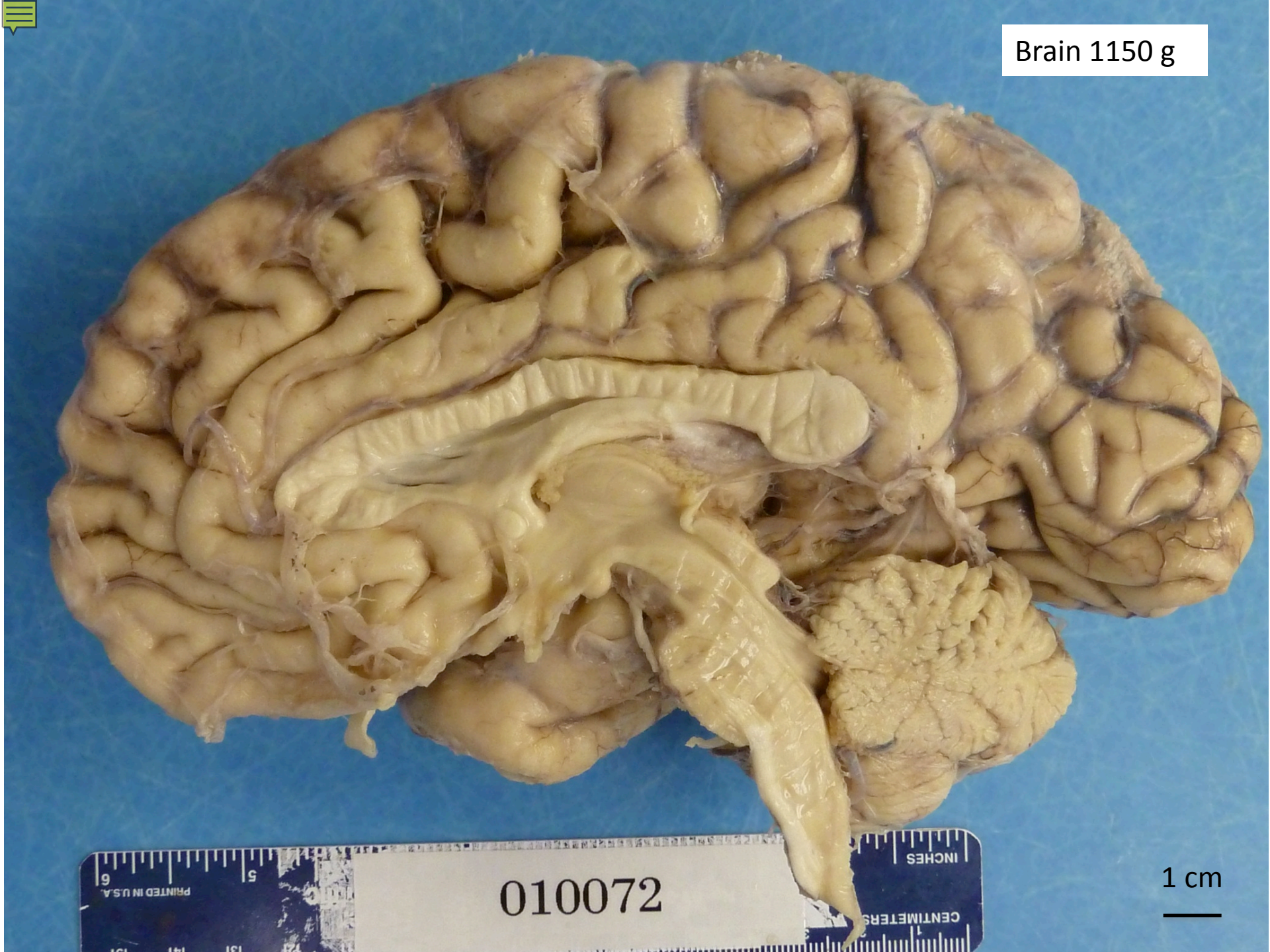
- Normal mental status
- Gait - wide-based, unsteady
- Dysarthria, decreased facial expression, slow saccades, mild impairment of upward gaze
- Mild symmetric lower extremity weakness (distal and proximal), spasticity
- Mildly reduced vibratory sense in the toes

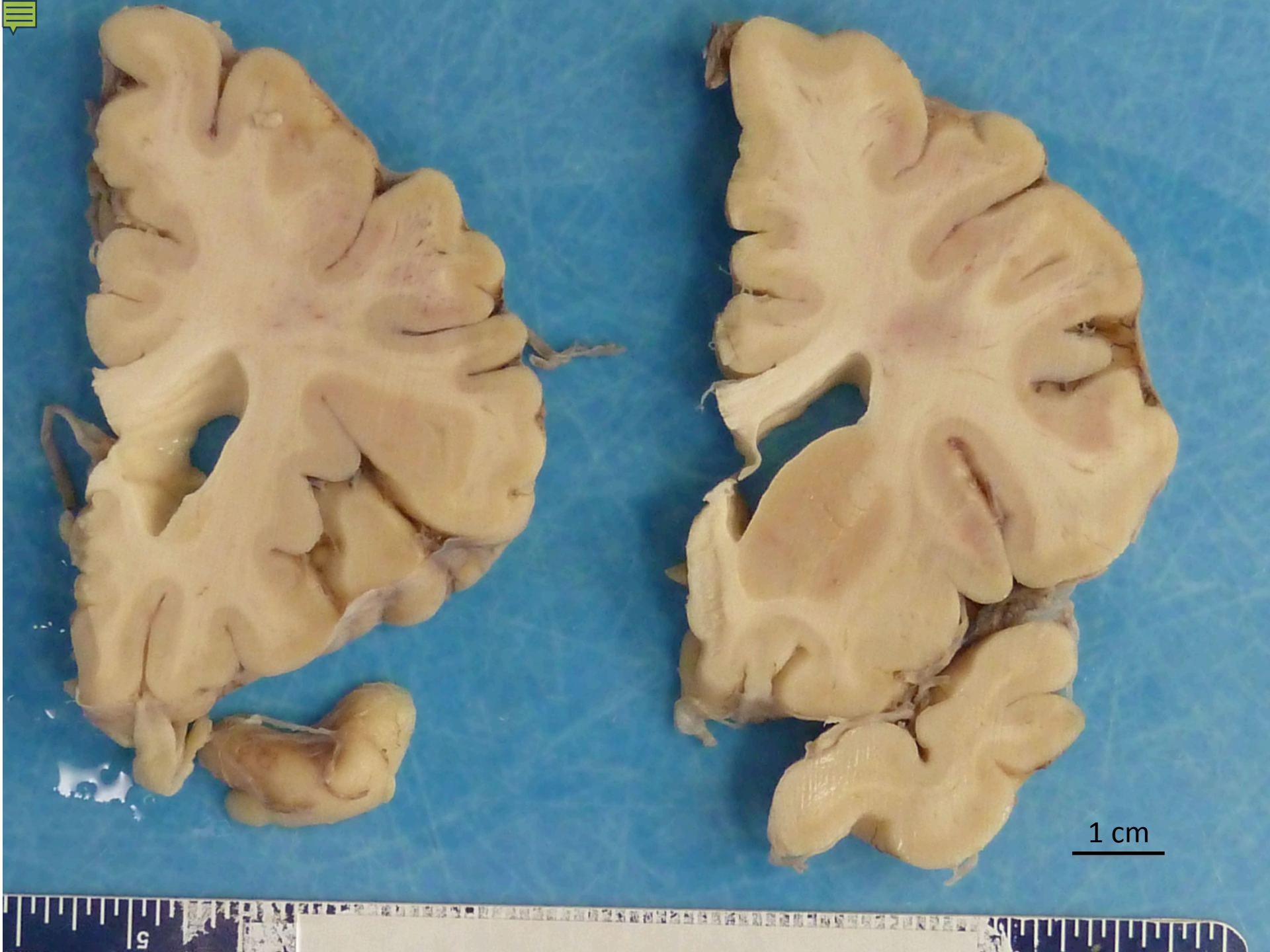
Progressive neurologic course: nystagmus, dysmetric saccades, ataxia, spasticity involving UE, worsening dysarthria and hypophonia, peripheral neuropathy

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

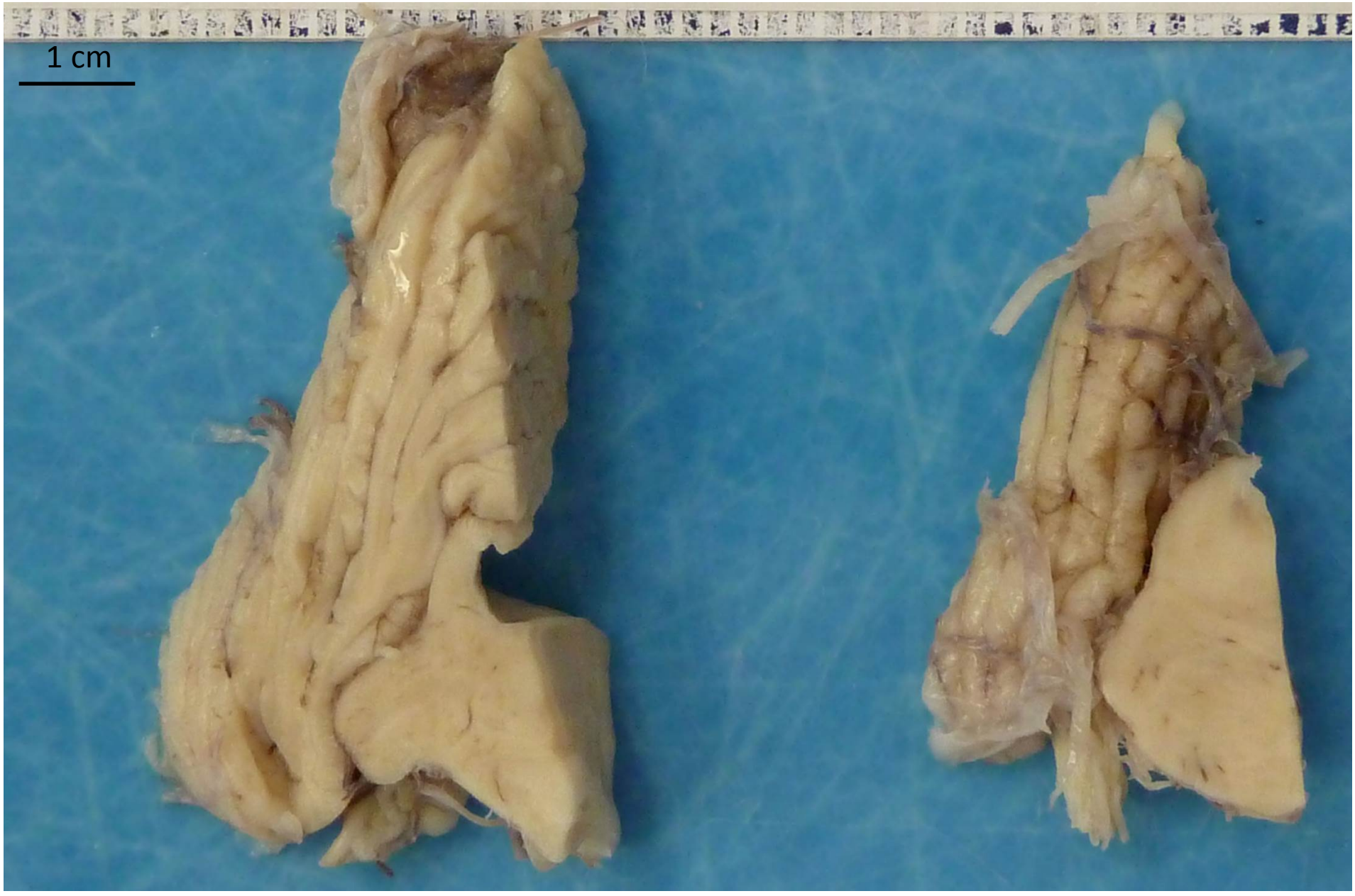
A diagnostic molecular test was performed

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

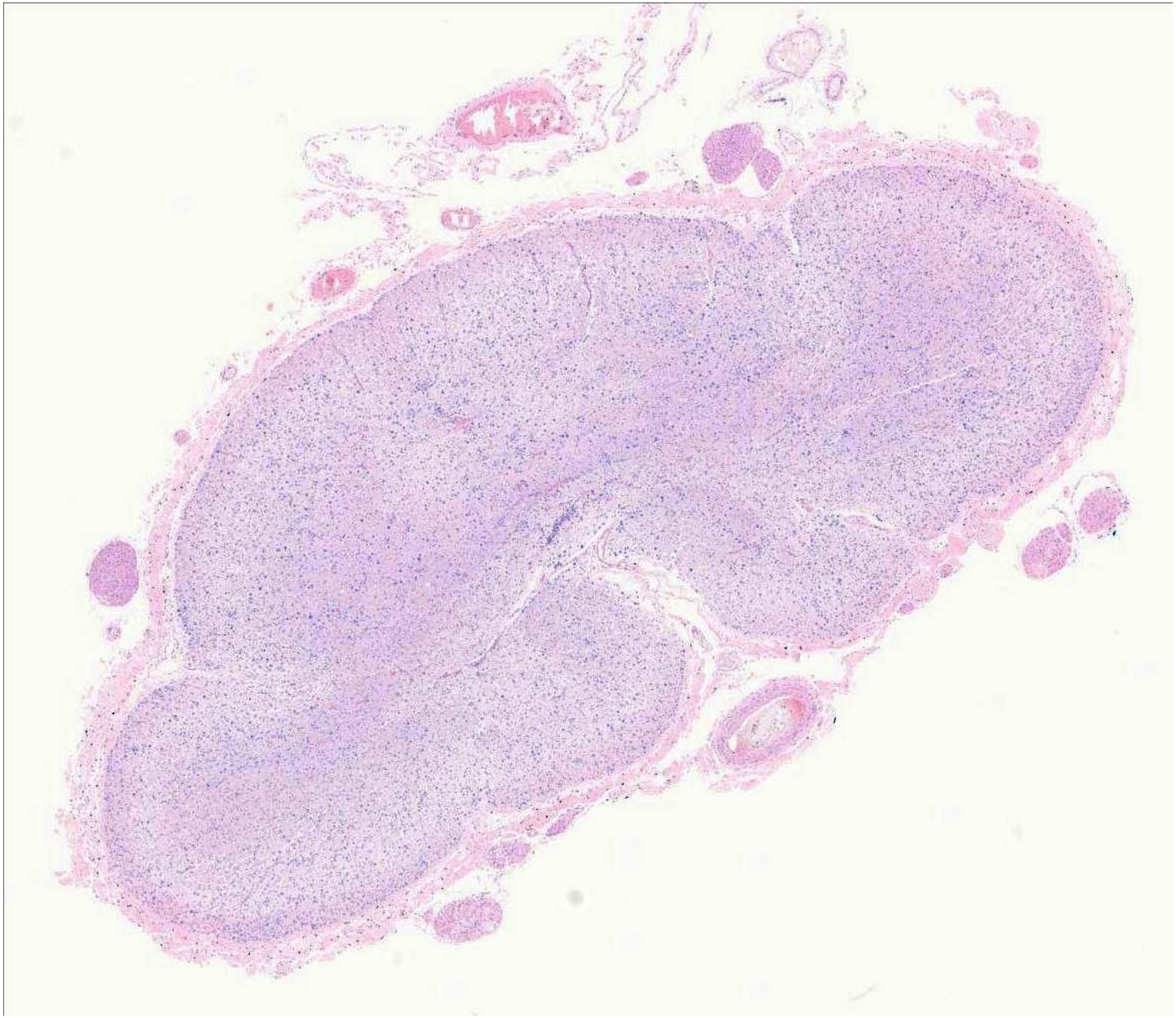

Brain 1150 g
010072
1 cm


1 cm

Cerebellum and pons



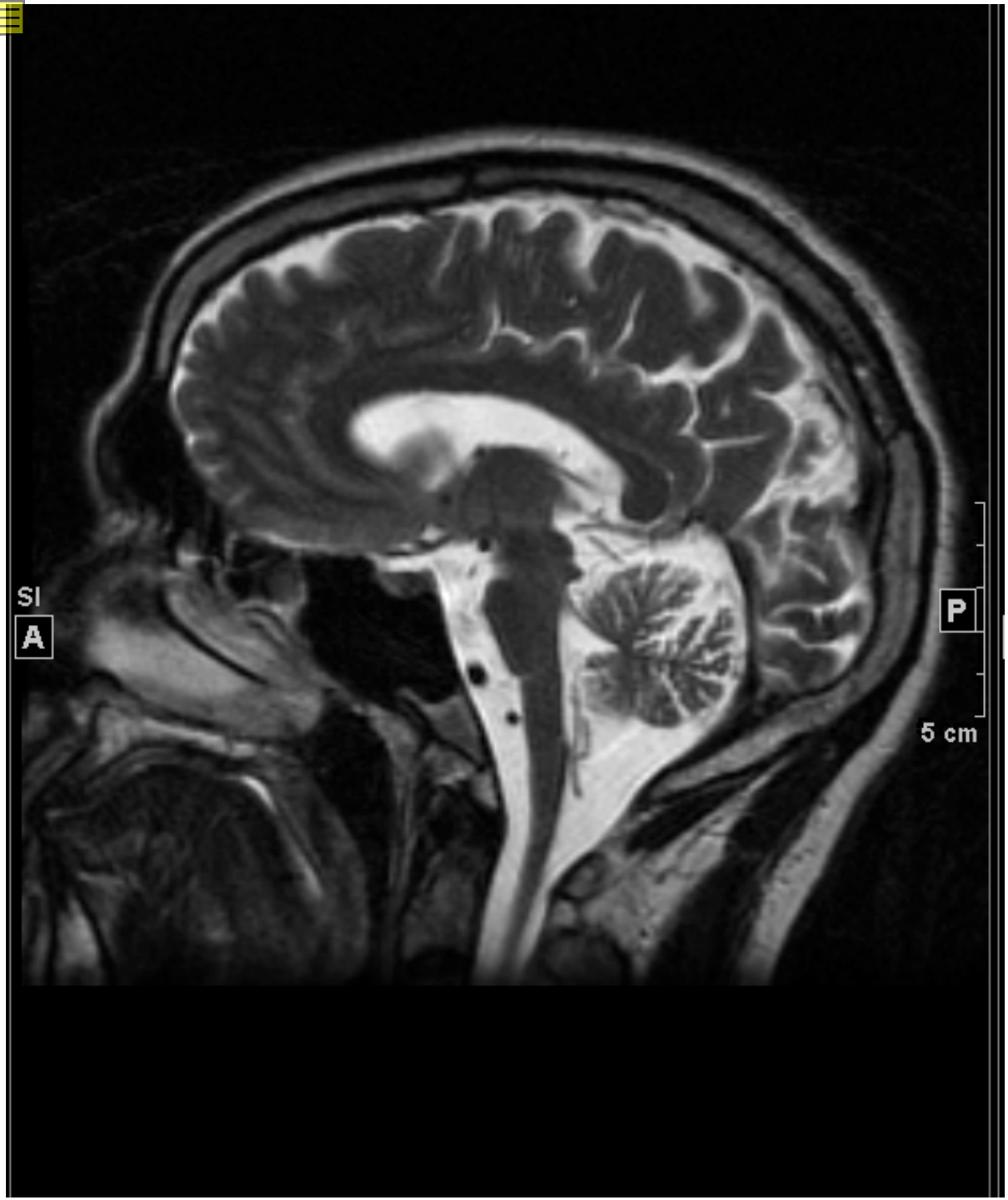
Spinal cord

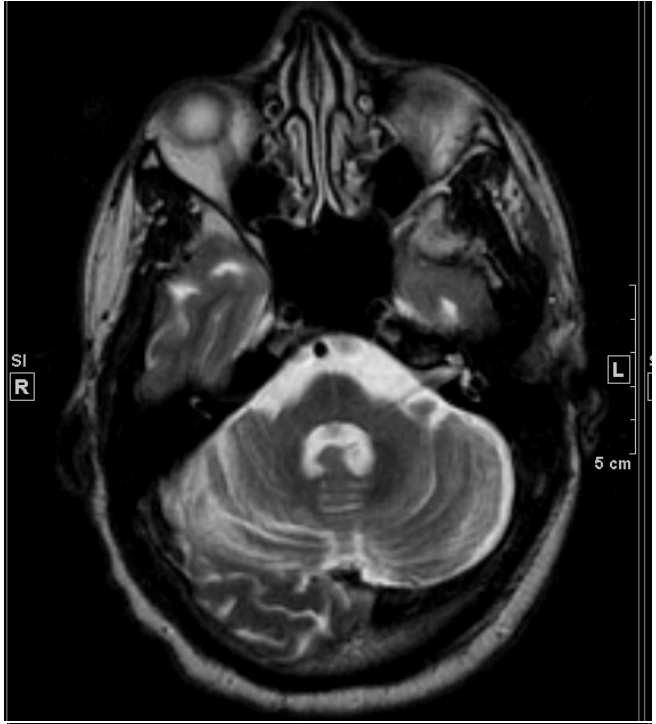


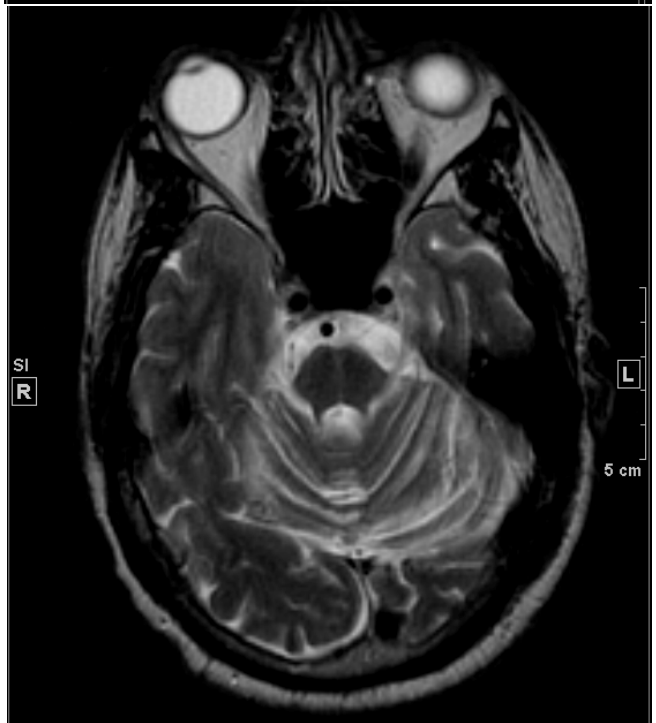
1. What was the diagnostic molecular test?

2. What is the diagnosis?

3. Is the neuropathology typical of this disorder?


SI
A
P
5 cm


SI
R
L
5 cm


SI
R
L
5 cm

Diagnostic molecular test

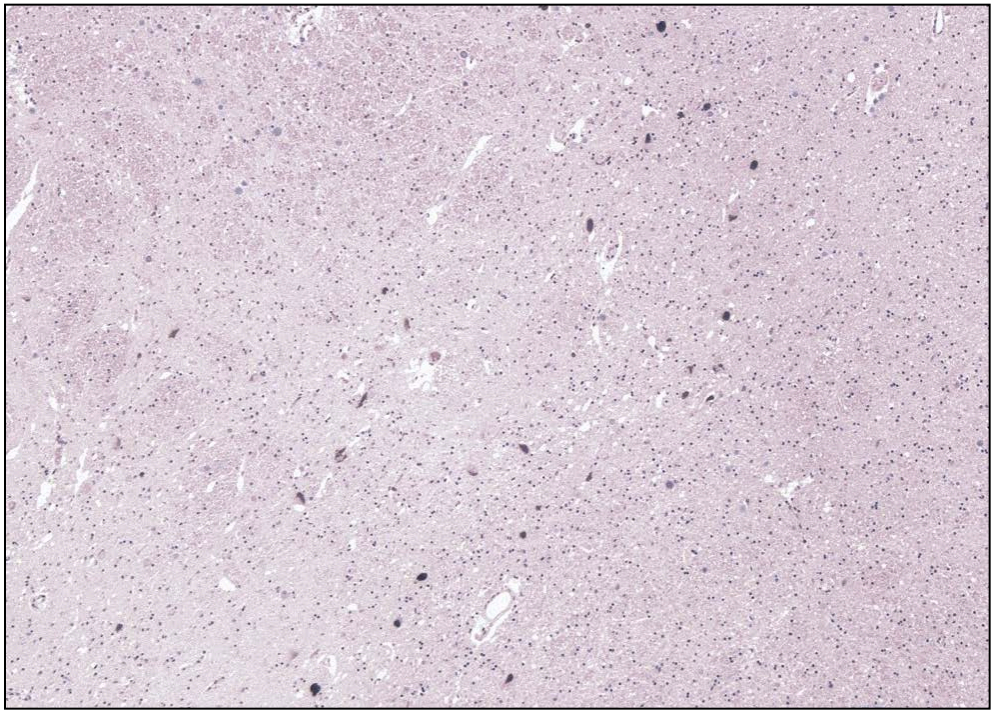
Testing for the CAG repeat expansion (Ataxia profile) was performed at **Athena Diagnostics, Inc**.

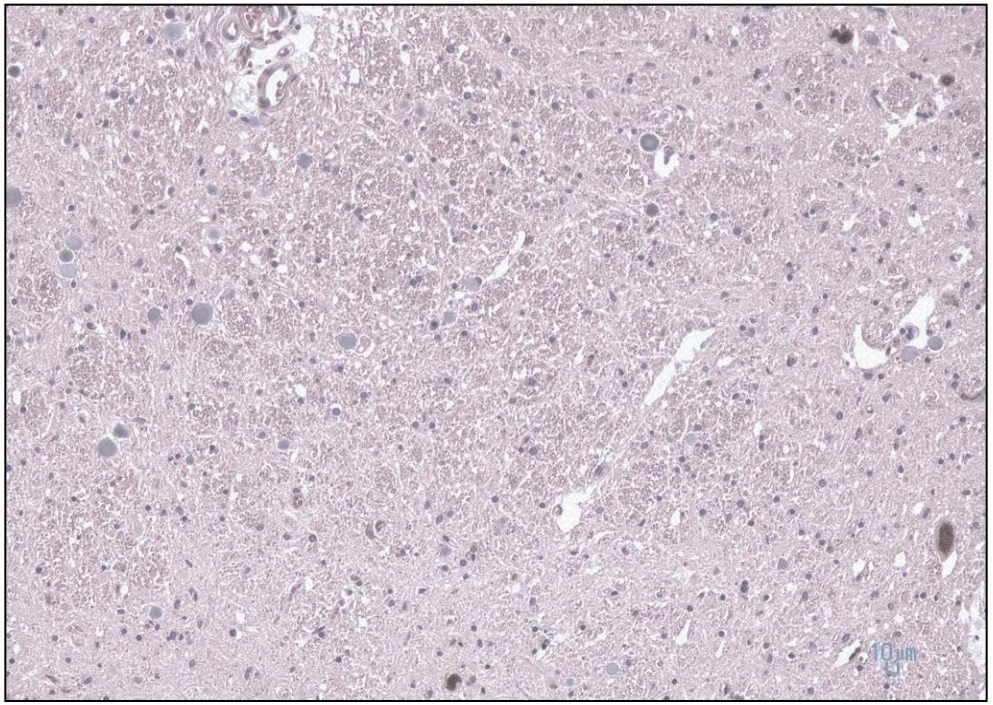
- SCA1 allele 1: 30 CAG repeats (N: < =34)
- SCA1 allele 2: 30 CAG repeats
- SCA2 allele 1: 23 CAG repeats (N: < =31)
- SCA2 allele 2: 23 CAG repeats
- MJD (SCA3) allele 1: 72 CAG repeats (N: < =40, B: 41-60)
- MJD (SCA3) allele 2: 38 CAG repeats
- SCA6 allele 1: 13 CAG repeats (N: < =18)
- SCA6 allele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

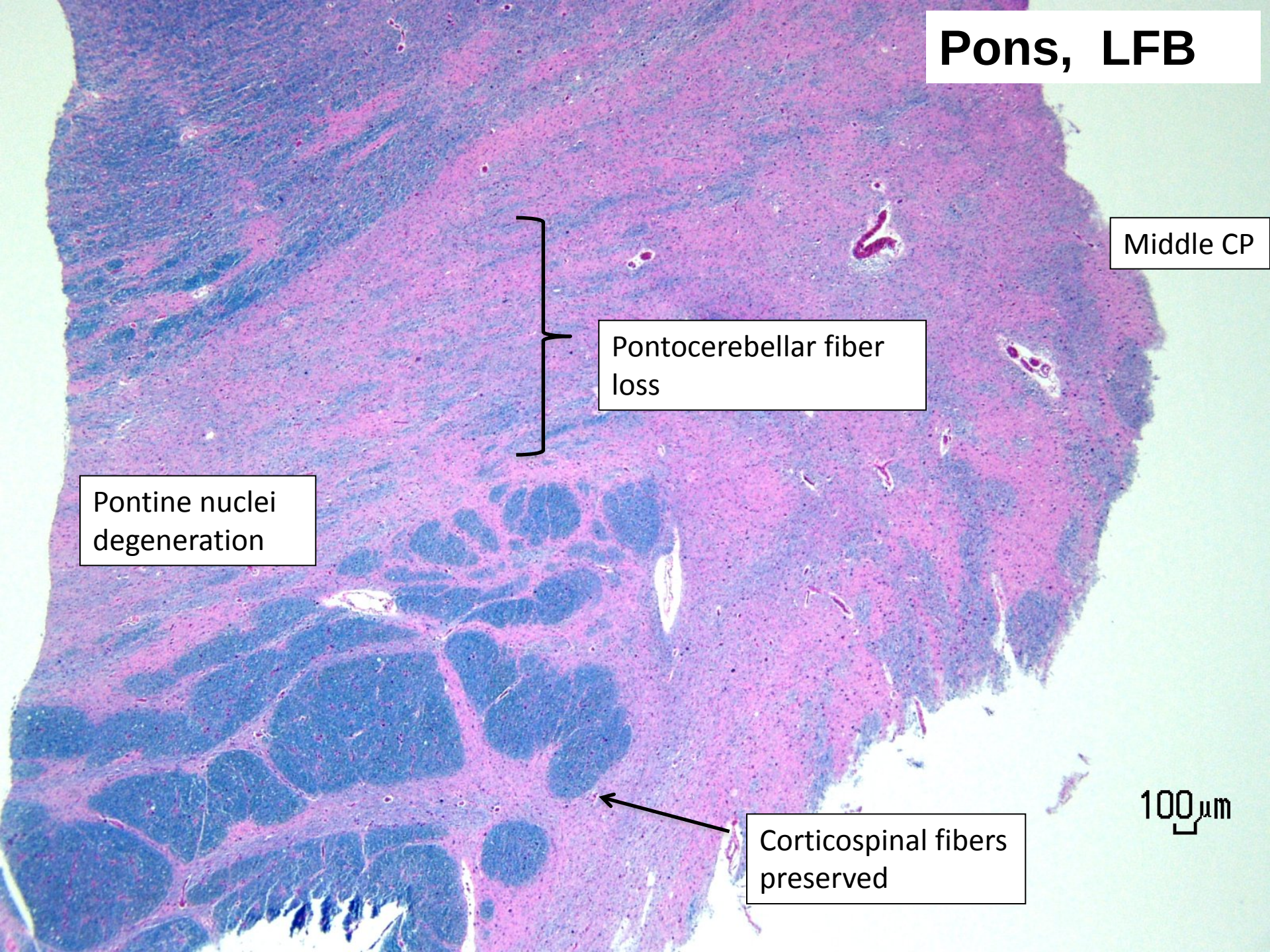
Neuropathology Findings

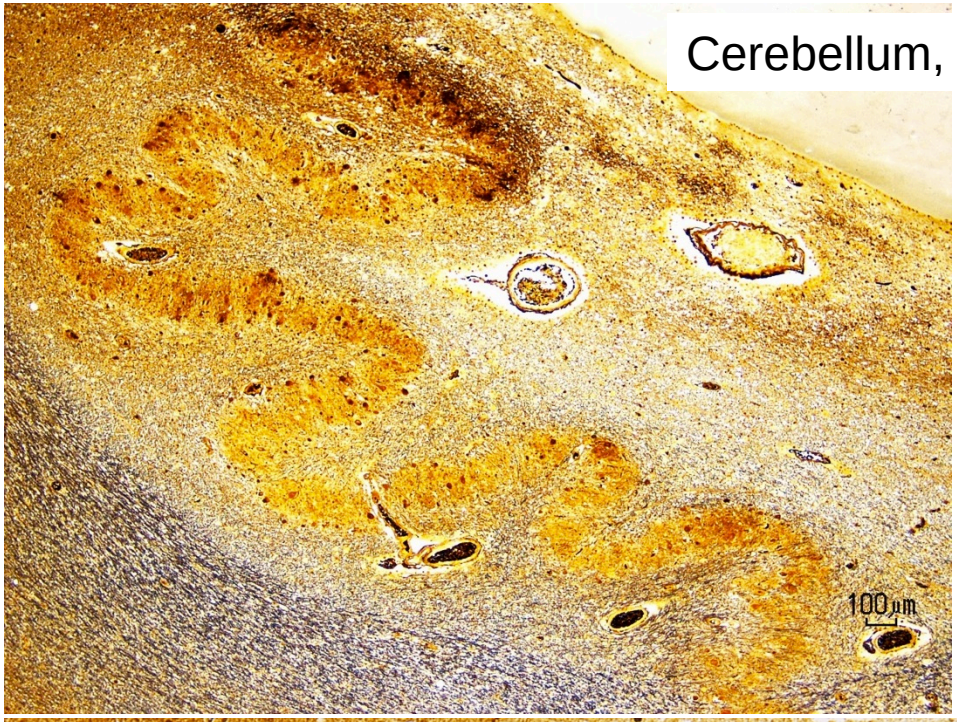
Midbrain with s. nigra

1 cm

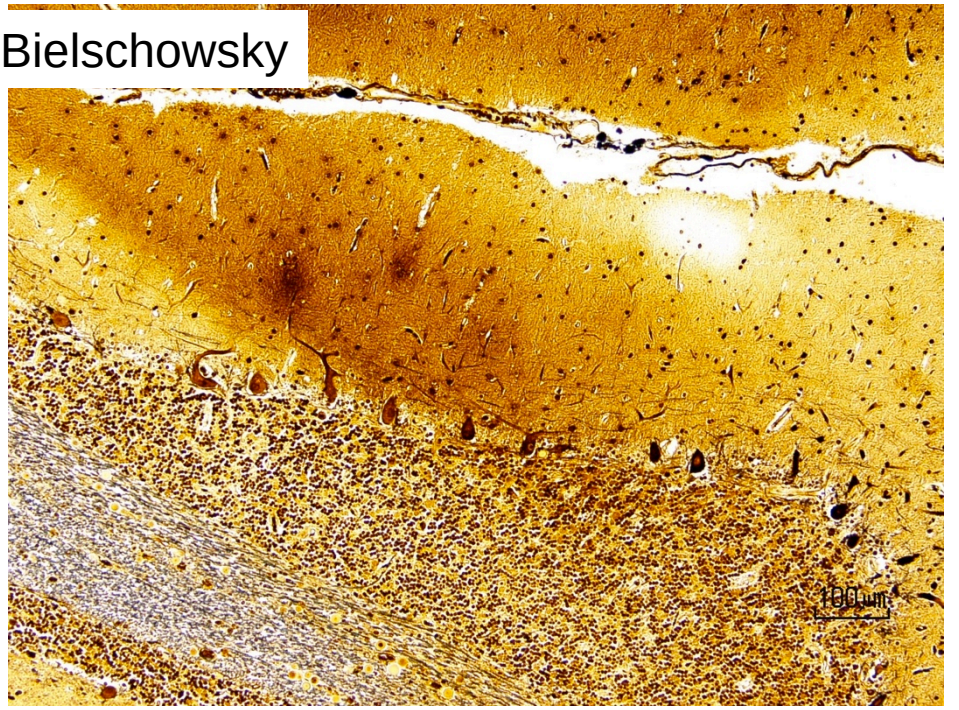


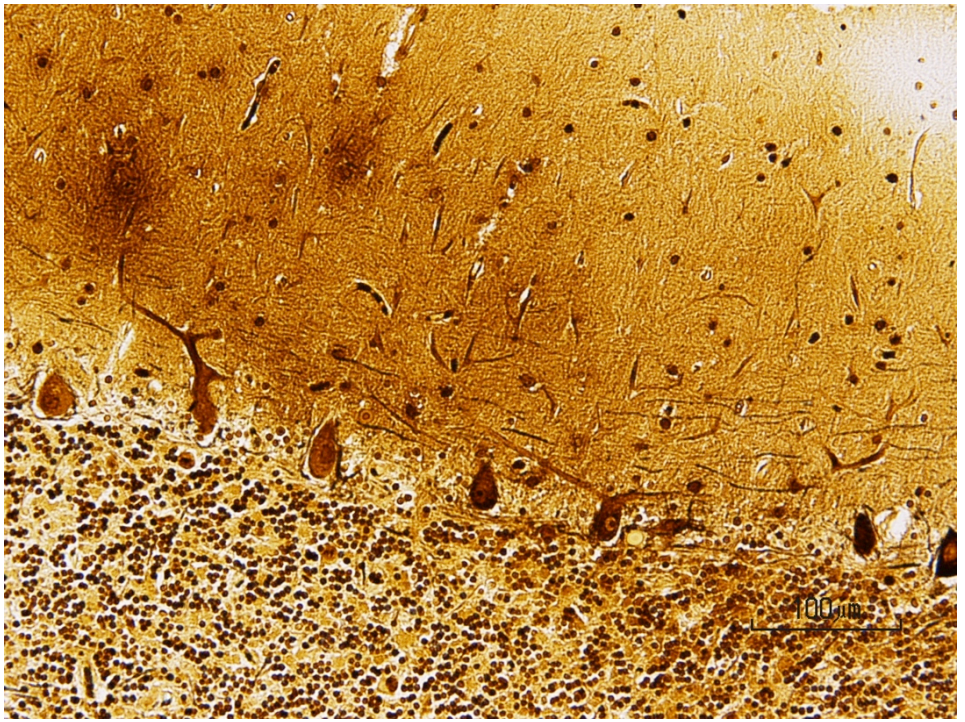


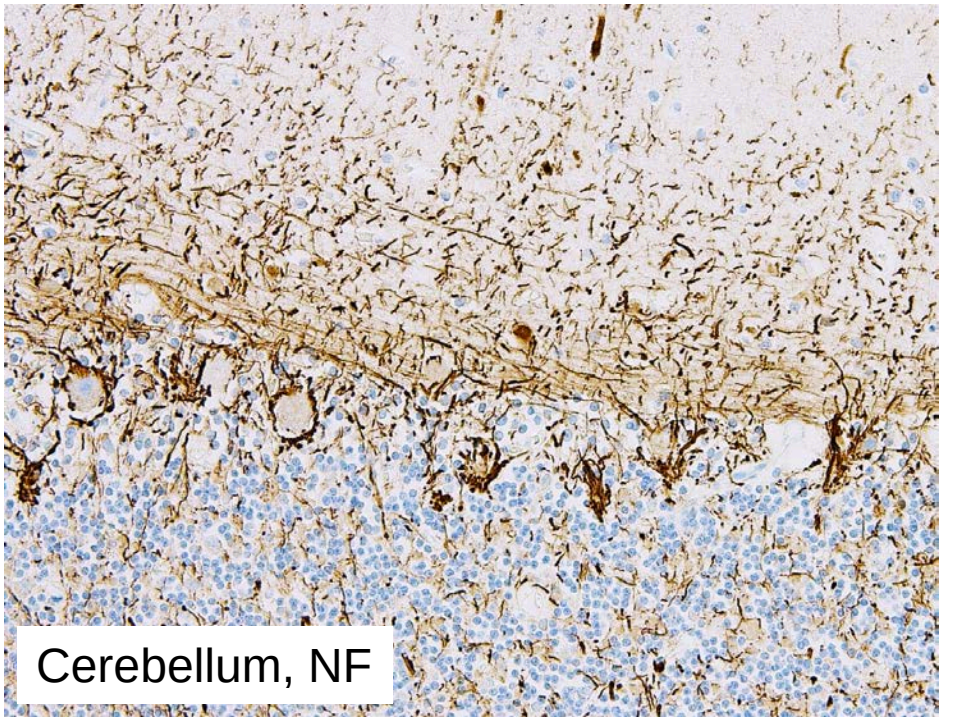

Pons, LFB
Middle CP
Pontocerebellar fiber loss
Pontine nuclei degeneration
Corticospinal fibers preserved
100 µm



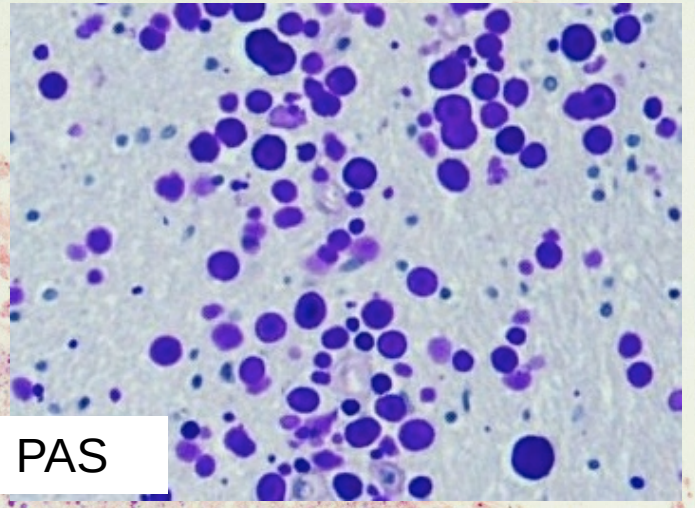
Cerebellum, Bielschowsky





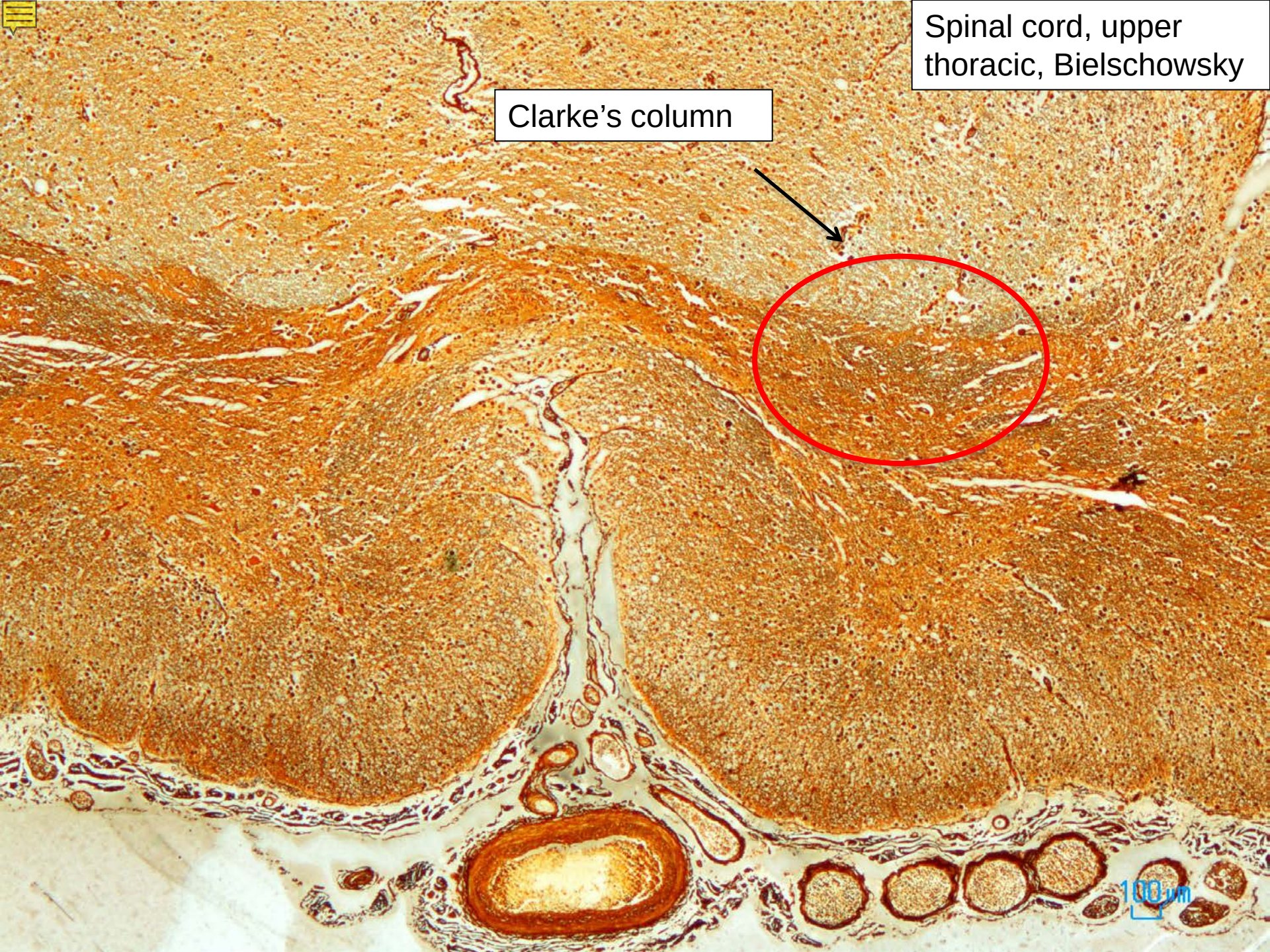


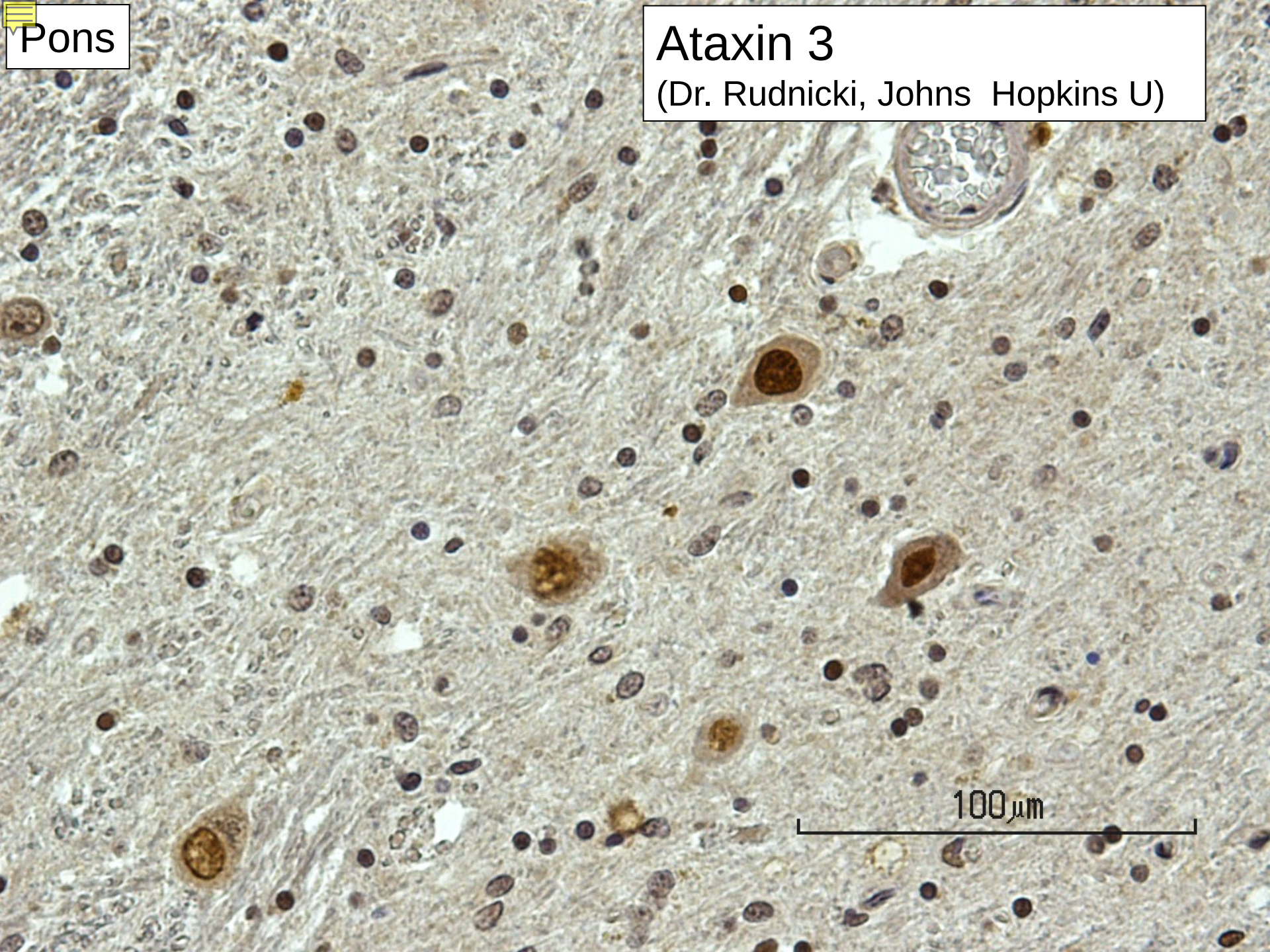
Cerebellum, NF



Spinal cord, upper thoracic

100 µm


Spinal cord, upper thoracic, Bielschowsky
Clarke's column
100 µm


Pons
Ataxin 3
(Dr. Rudnicki, Johns Hopkins U)
100μm

Diagnosis

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

with

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

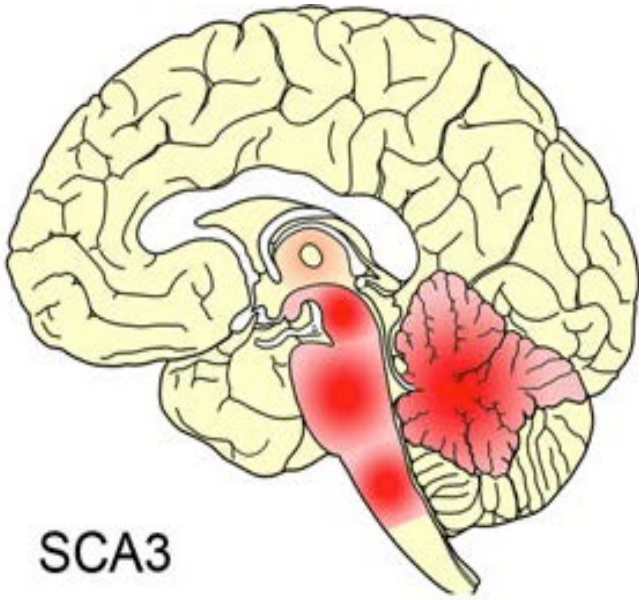
Hereditary ataxias

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

AD	AR	X-link	Mit
1. SCA 1-41 Repeat expansion, > CAG, mutations • Cerebellar cortical atrophy, • OPCA • Spinocerebellar degeneration **2. DRPLA** CAG expansion in atrophin-1 (12p) - 49-75 (n – 7-23) • Chorea, myoclonic epi, dementia (simul of HD) • Neuronal loss: DN, GP, subthalamic, caudate, putamen, SN, inf olives • Atrophy of sup CP • Degeneration of post spinal columns and spinocerebellar tracts **3. Episodic ataxias EA1-8** **4. Dominant ataxia s-mes**	**1. Friedreich ataxia** 9q *FRDA* – frataxin: 95% - GAA 500-1000 (n- 6-34) Degeneration: • Spinal cord - post columns, distal spino-cerebellar and pyramidal tracts, Clarke's • DRG, large myelin axons from post roots • Medulla: accessory cuneate and gracile n., sup. olives • 2* ischemic changes (cardiomyopathy) **2. Ataxia w vit E def** α-tocopherol transfer protein, similar to FA **3. Mitochondrial recessive ataxia s-me** Mut POLG – DNA-polymerase-γ: depletion of mt DNA in PN and skeletal muscle: a. SCAE – cerebellar and sensory b. SANDO – sensory ataxia w. periph neuropathy, dysarthria and ophthalmoplegia **4. DNA repair s-mes (AT, XP, Cockayne ERCC, MRE11A)** **5. SCAR 1-20**	**1. FXTAS** CGG expansion in 5' UTR of FMR1 - 55-200 – premutation • Cortical atrophy • Loss of Purkinje cells, • Axon and myelin loss in wm • Intranucl inclusions (N, A) **2. SCAX 1-5** **3. Congenital and recessive diseases with cerebellar aplasia**	**1. MERFF** tRNA (lys, leu) **2. MELAS** tRNA leu **3. NARP** ATPase 6 gene

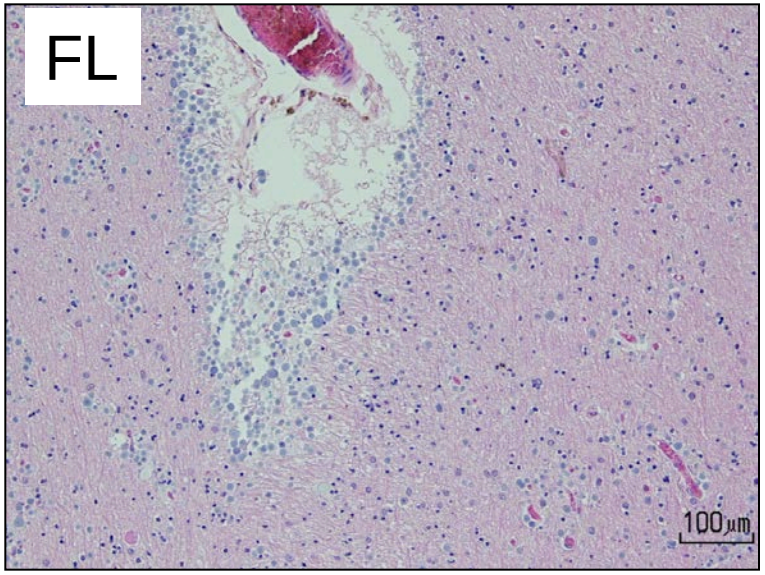
Spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD)

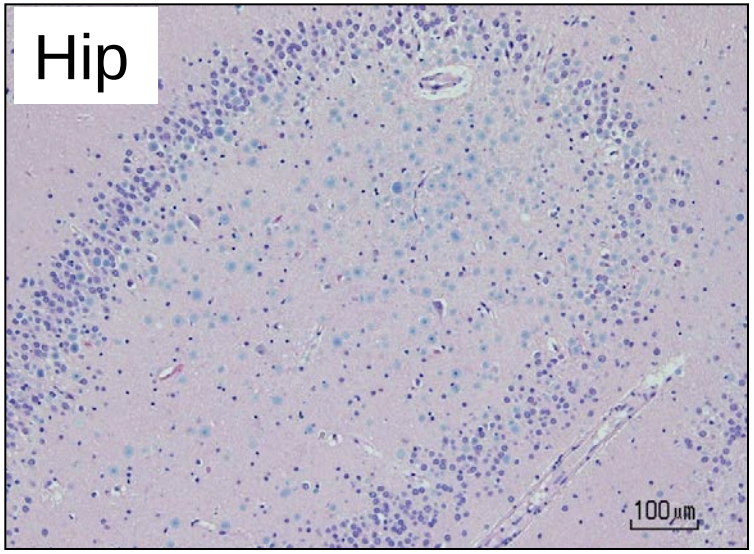
- The most frequent subtype of AD SCA. Originated from founders in the Iberia Peninsula, who migrated to the Azores
- CAG repeat expansion > 55 units in the *ATXN3* gene, 14q32.1 region
- Intranuclear aggregates of ataxin-3, proteasome subunits and transcription factors (TBP and CBP)
- The clinical variability: 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'scolumns, +/- 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?





- Adult polyglucosan body disease: AR or sporadic a/w the diffuse accumulation of abnormally branched glycogen in polyglucosan bodies.
- 5^{th} – 7^{th} 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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Dushyant Purohit, MD

Sergey Zhadanov, MD, PhD

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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.
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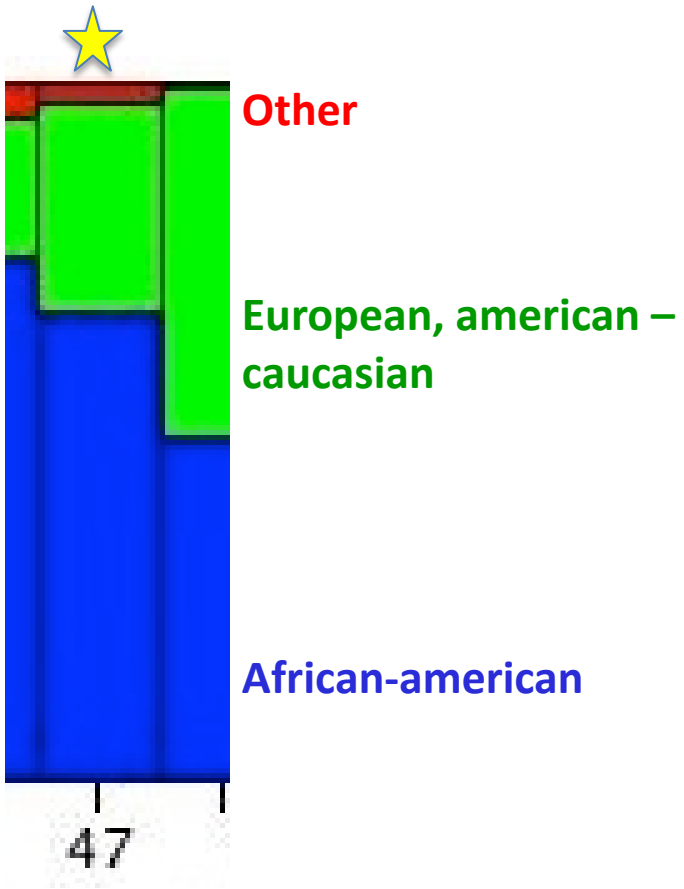
6. Takiyama Y et al. Evidence for intergenerational istability in the CAG repeat in the MJD1 gene and for conserved haplotypes at flanking markers amongst Japanese and Caucasian subjects with Machado-Joseph disease. Hum Mol Genet. 1995;4:1137–1146.
7. Urkasemsin et al. Mapping of Purkinje neuron loss 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