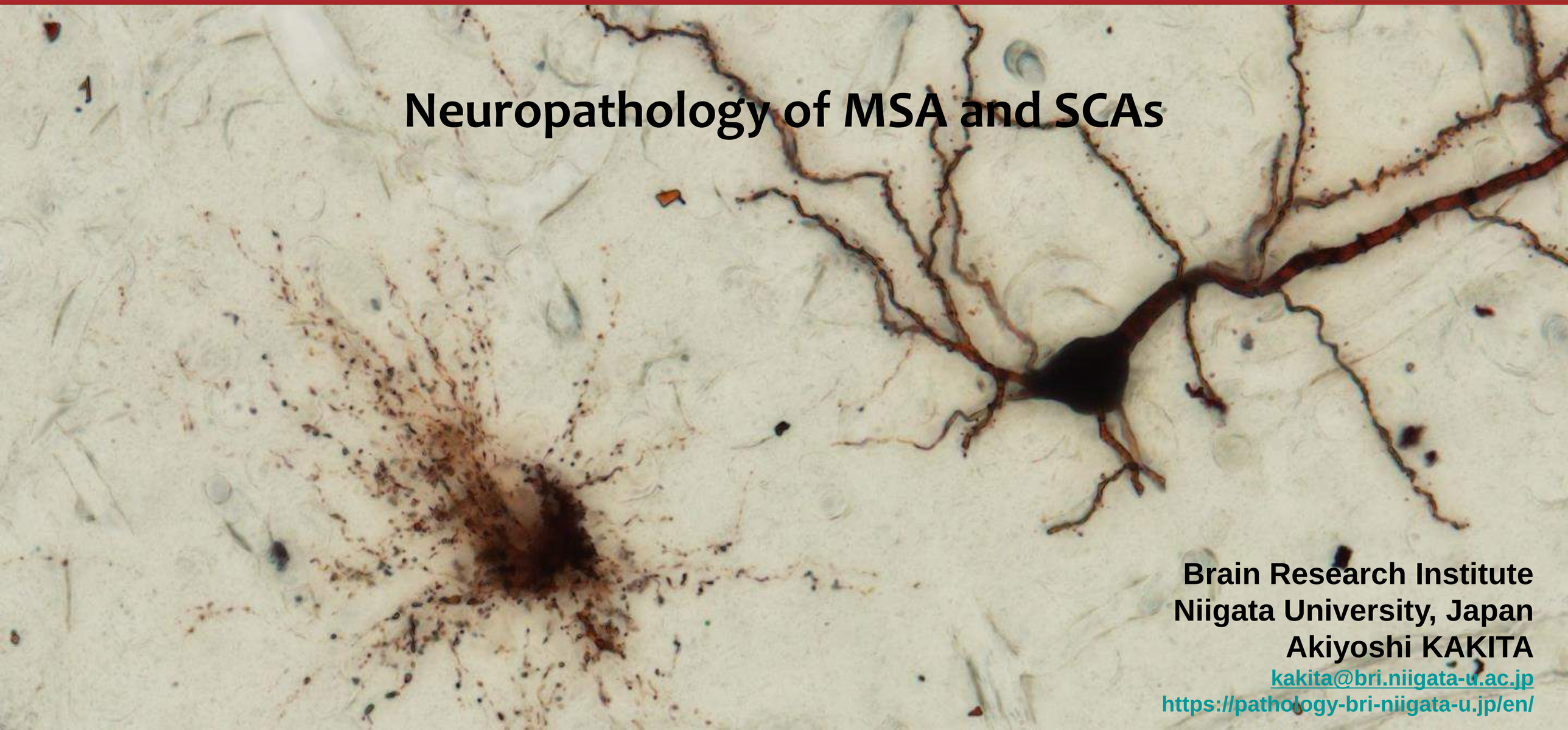
Neuropathology and Neuroimaging Integrated Education Course for Movement Disorders
February 16-17, 2024 • Seoul, Korea
International Parkinson and Movement Disorder Society Asian & Oceanian Section

Neuropathology of MSA and SCAs



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Presentation outline

1 pathologic features of a representative α-synucleinopathy
MSA – Sporadic disorder

2 for a better understanding of systemic degeneration ....
Cerebellum: anatomy

3 pathologic features of spinocerebellar ataxias
Autosomal Dominant disorders
SCA6, DRPLA, SCA3/MJD, SCA2, SCA31

4 pathologic features of spinocerebellar ataxias
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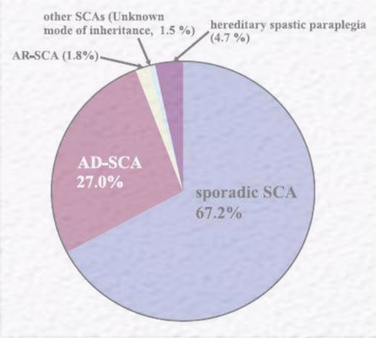
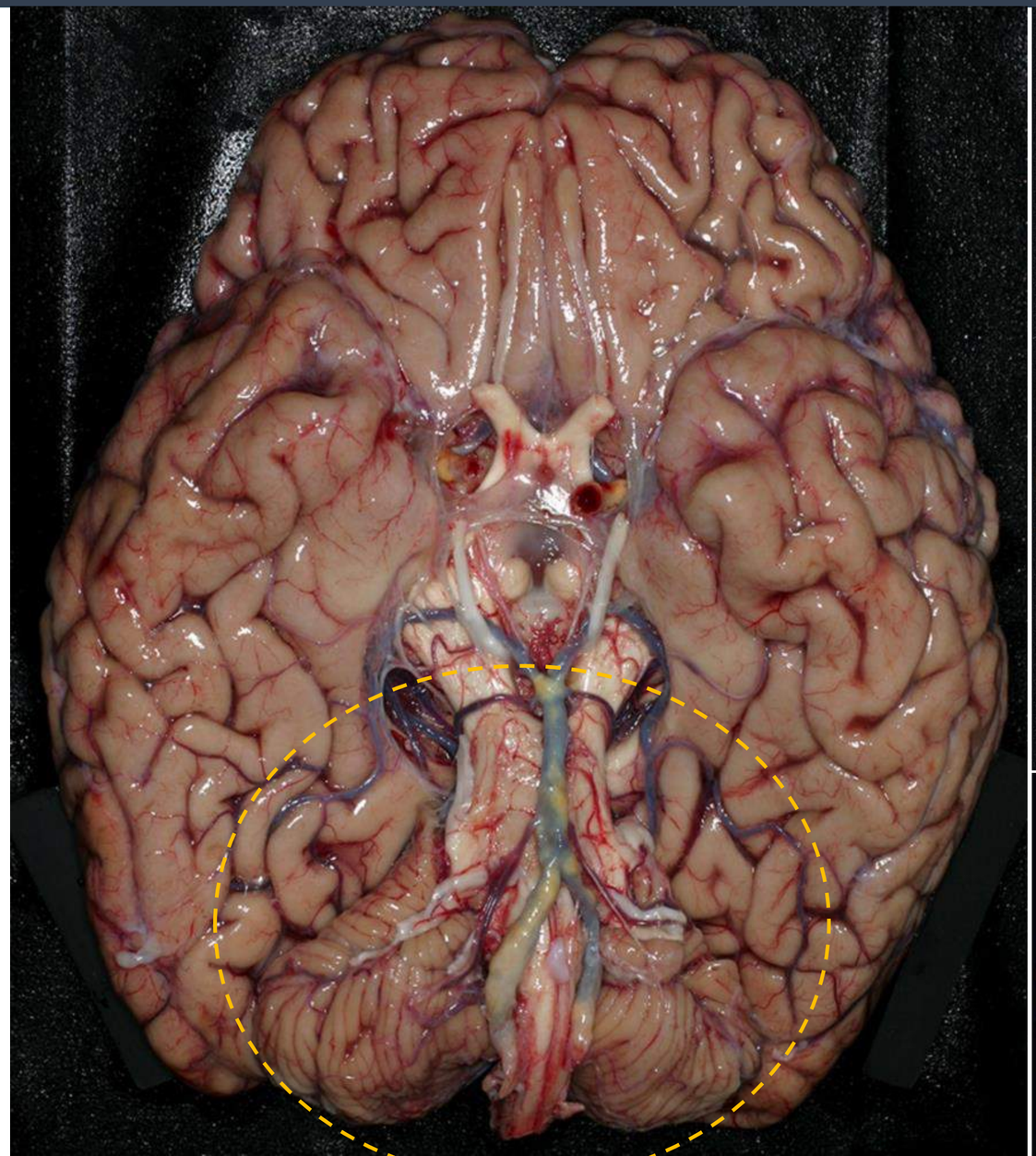
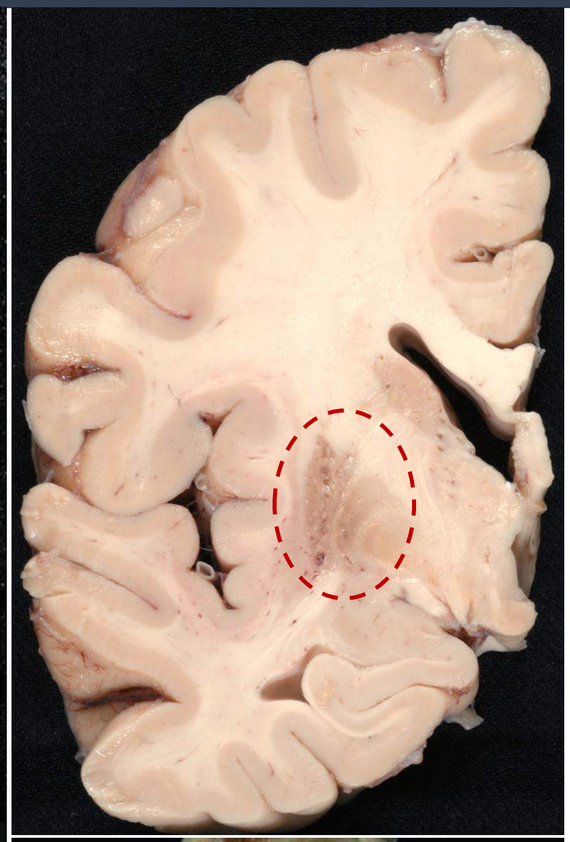


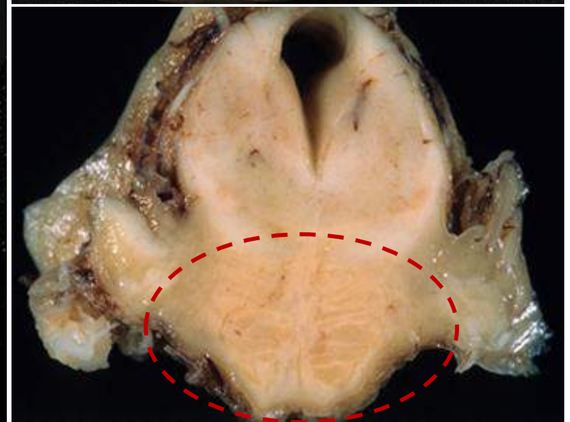
All the presenting cases were experienced at the Brain Res Inst, Niigata Univ, Japan

Multiple System Atrophy

- A sporadic adult-onset neurodegenerative disorder
- autonomic dysfunction, cerebellar ataxia, and parkinsonism, each due to degeneration of the autonomic, olivopontocerebellar, and striatonigral systems
- accumulation of α-synuclein protein

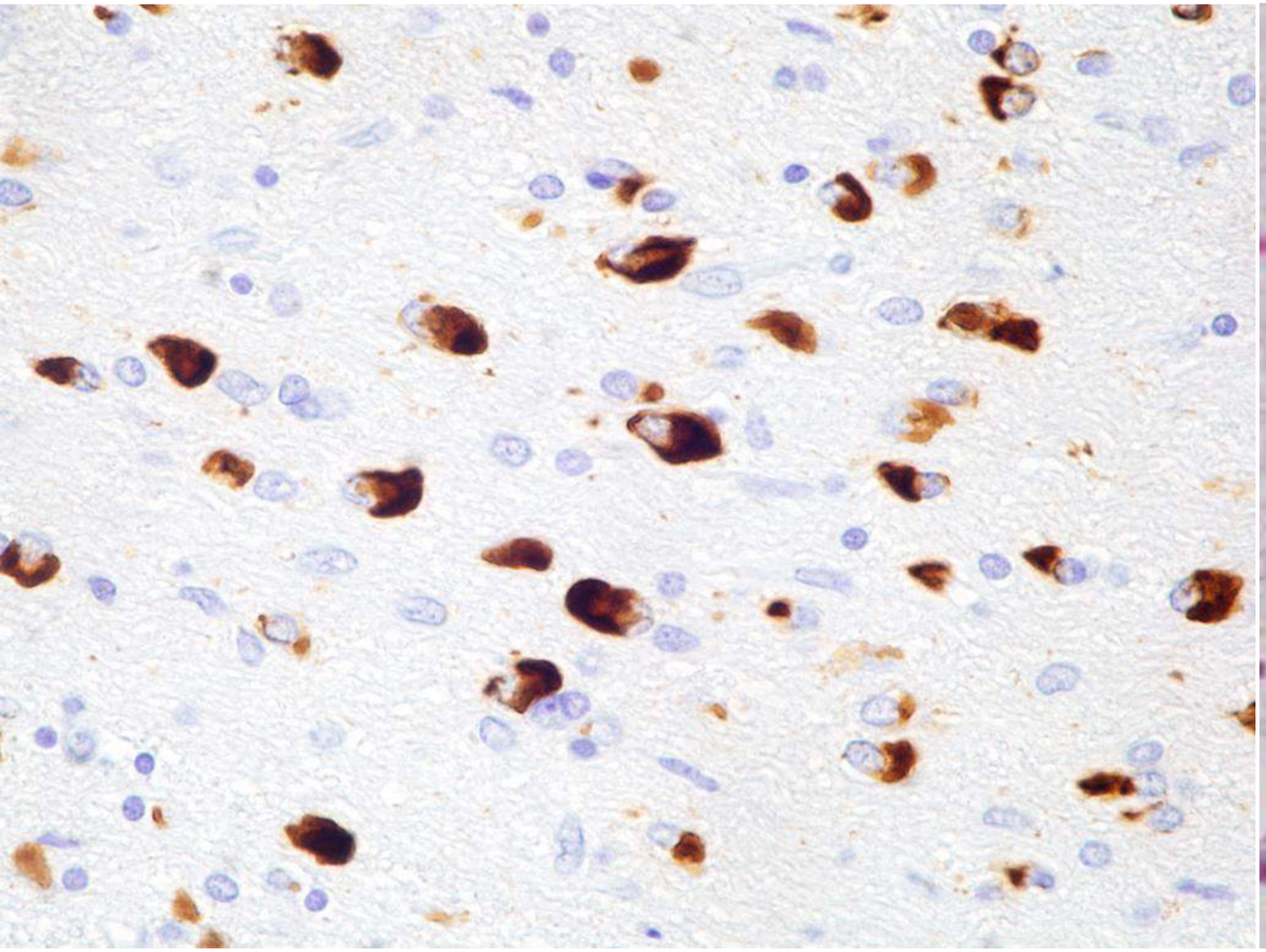




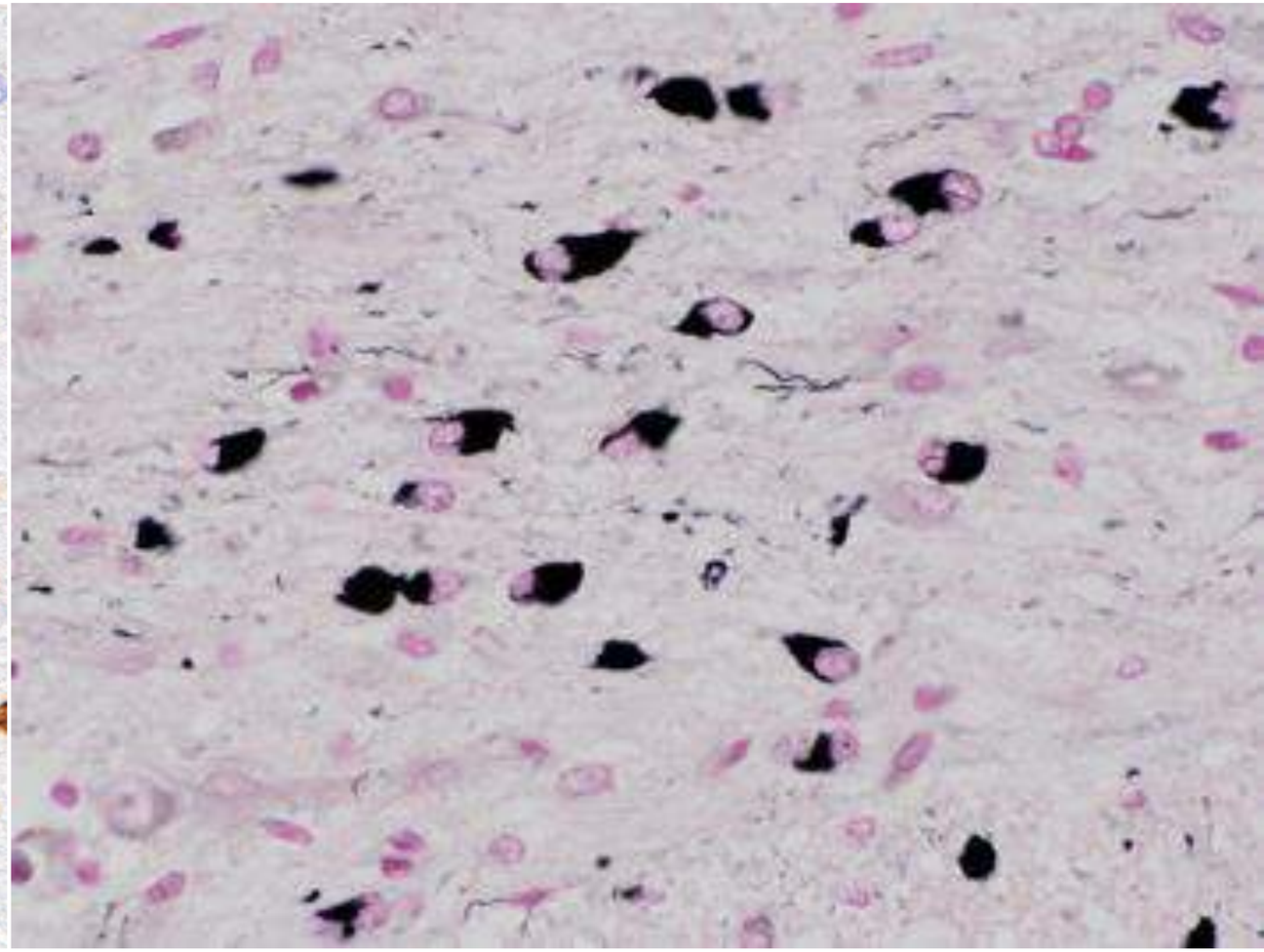


MSA: glial cytoplasmic inclusions

α-synuclein-immunostain



Gallyas-Braak silver stain



“argyrophilia”

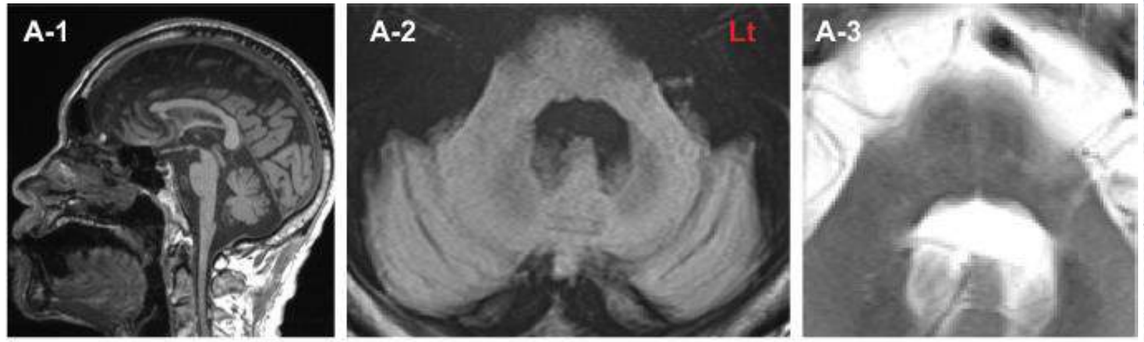
MSA: recently experienced case

Marked laterality of olivopontocerebellar pathology in an autopsied patient with MSA: Implications for degeneration and α-synuclein propagation

Misato Ozawa ,[1,2] Rie Saito ,[1] Takuya Konno,[3] Reiji Koide,[2] Shigeru Fujimoto ,[2] Osamu Onodera ,[3] Akiyoshi Kakita[1]

INTRODUCTION

Multiple system atrophy (MSA) is a sporadic adult-onset neurodegener-



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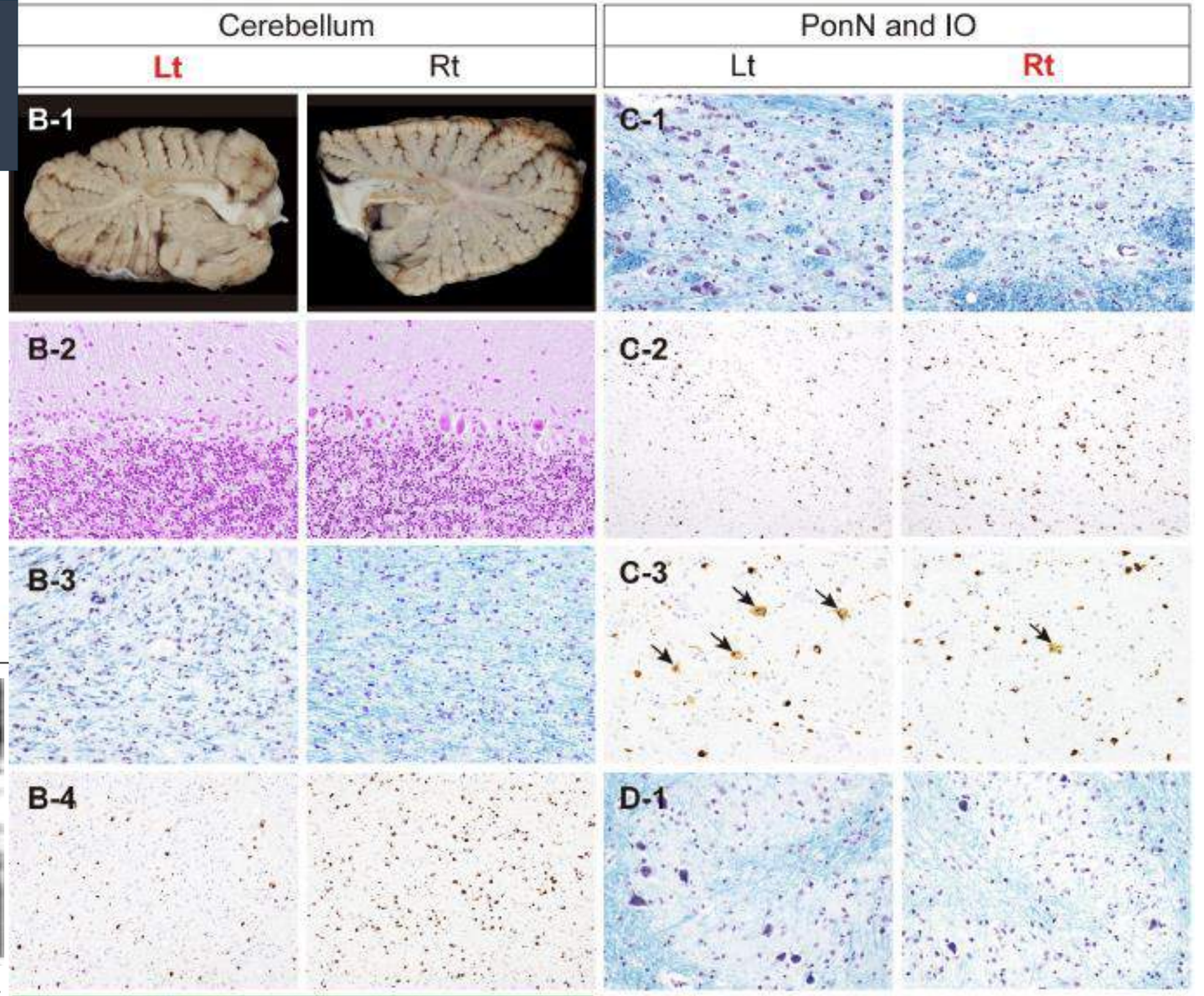
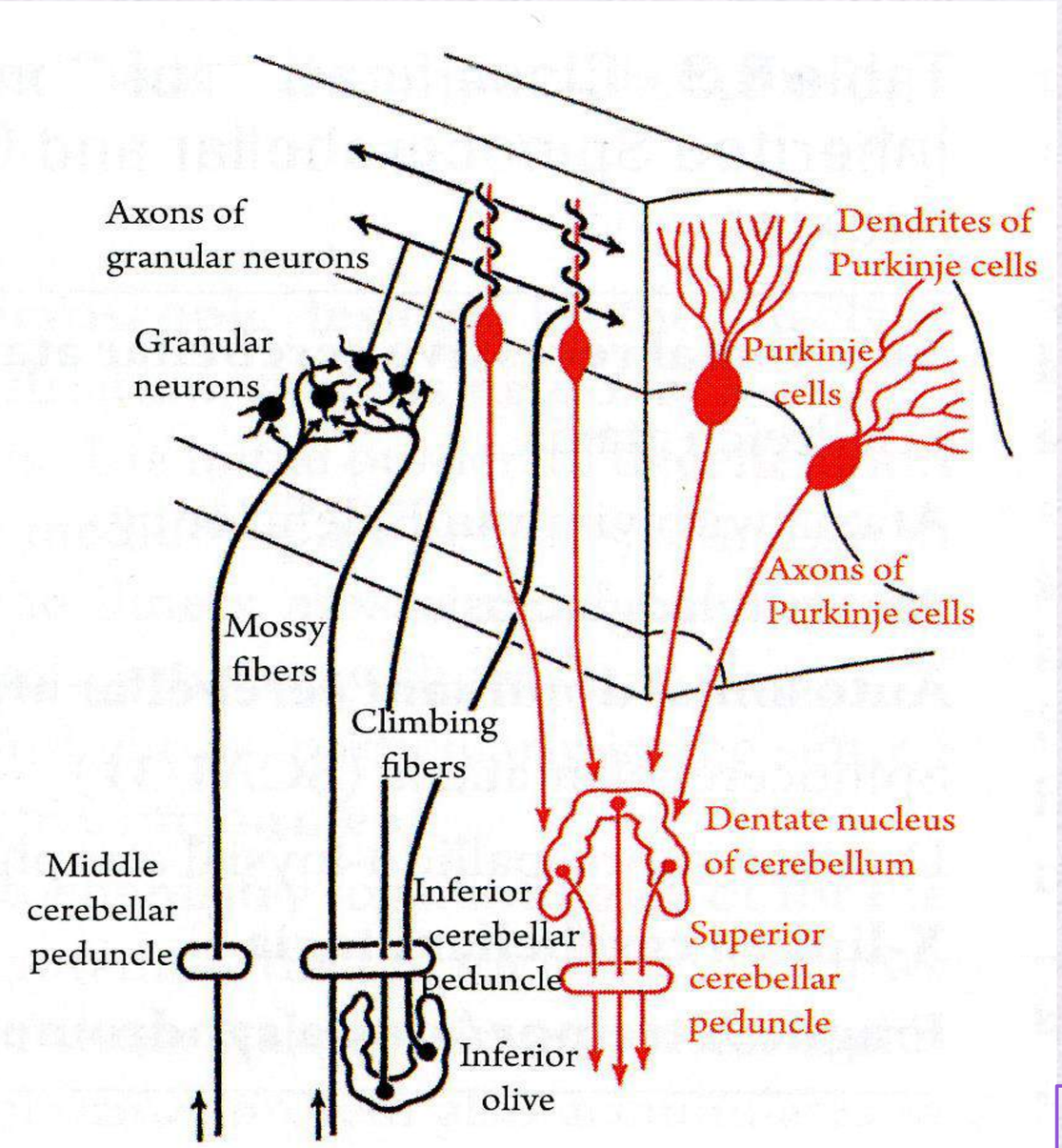


E	Degeneration	α-syn (GCI)	α-syn (NNI,NCI)
Cerebellar cortex	**Lt** > Rt 3/2	None	None
Cerebellar white matter	**Lt** > Rt 3/3	Lt < **Rt**	NA
Pontine nucleus	Lt < **Rt** 1/2	Lt < **Rt**	**Lt** > Rt
Inferior olivary nucleus	Lt < **Rt** 1/2	Lt < **Rt**	**Lt** > Rt

Cerebellum: anatomy



cerebellar cortex
- Purkinje cells
- granule cells

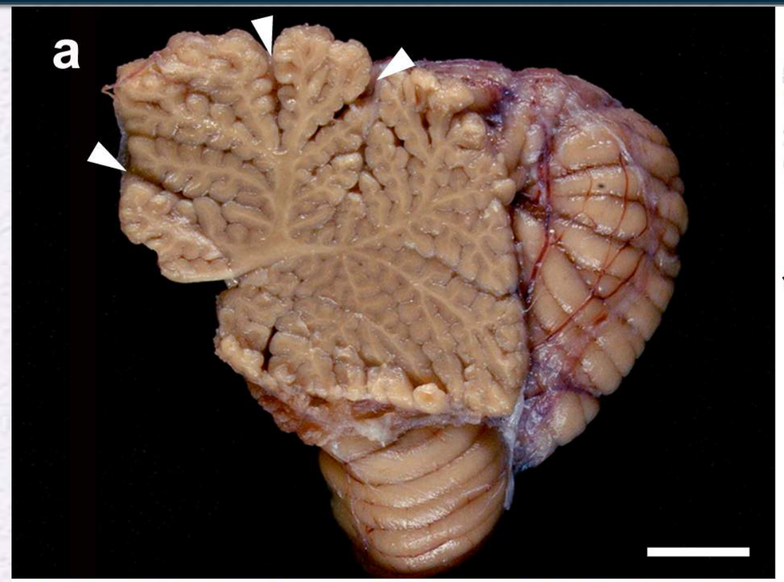
cerebellar "efferent" fibers
- dentate nucleus → red nucleus
  - superior cerebellar peduncle

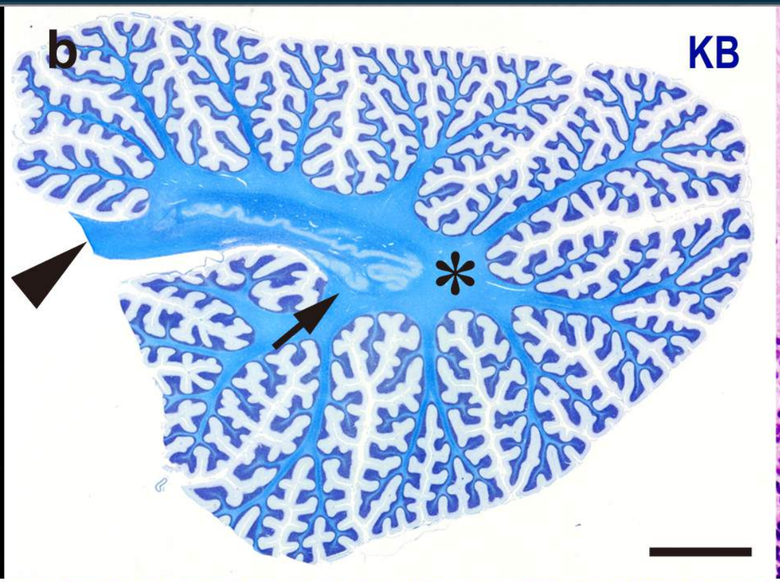
cerebellar "afferent" fibers
- pontine nucleus
  - middle cerebellar peduncle
- inferior olivary nucleus
- Clark's nucleus
- accessory cuneate nucleus
  - inferior cerebellar peduncle

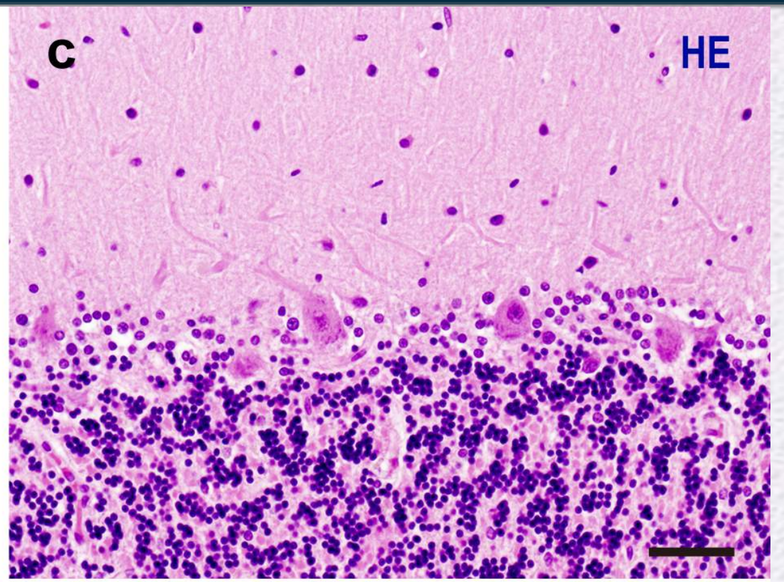
Escourolle and Poirier's
Manual of Basic Neuropathology

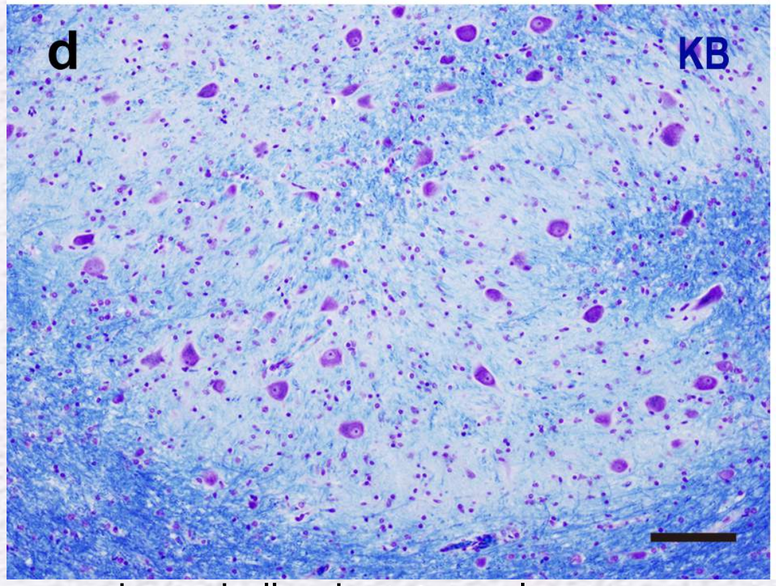
Control

cerebellum and efferent/afferent nuclei

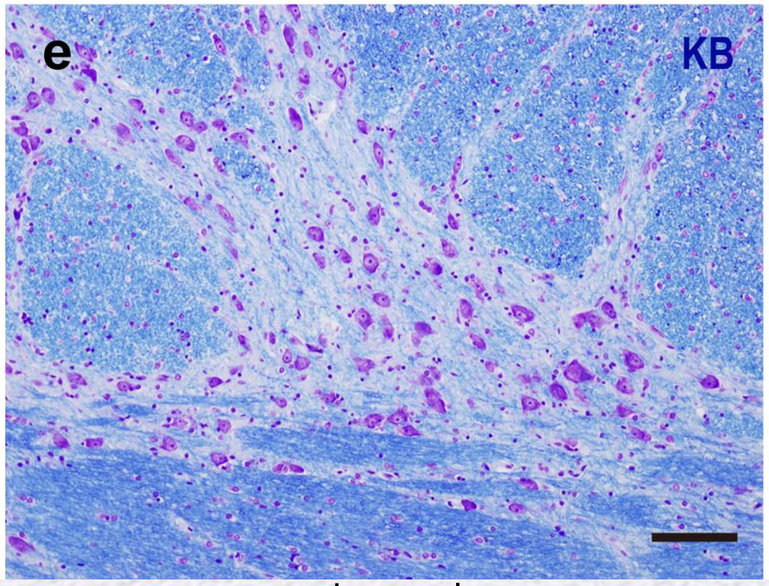




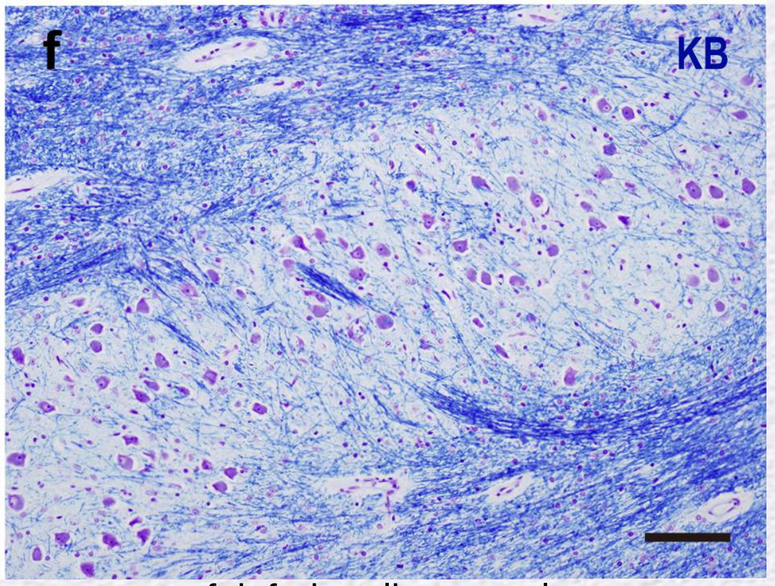




d: cerebellar dentate nucleus
"efferent"



e: pontine nucleus
"afferent"



f: inferior olivary nucleus
"afferent"

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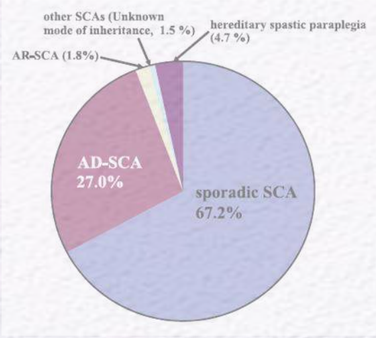

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SCAs: lesional distributions

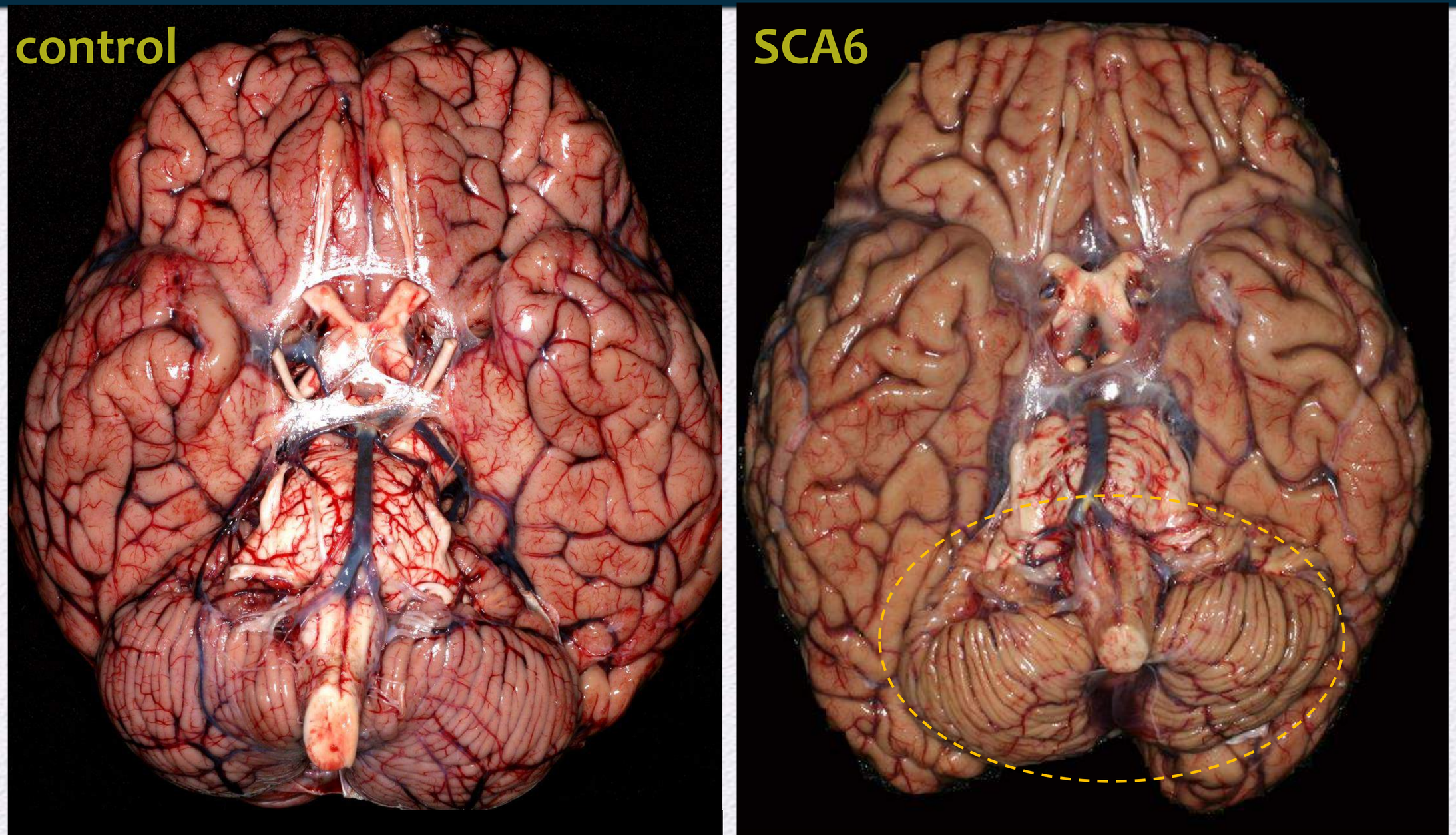
			SCA2	SCA3/MJD	SCA6	DRPLA	SCA31
Cerebellar system	Cerebellar cortex	Purkinje cells	●		●		●
		granule cells			●		
	“efferent” tracts	dentate nucleus		●		●	
		red nucleus	●			●	
	“afferent tracts	pontine nucleus	●	●			
		inferior olivary nucleus	●				
		Clarke nucleus	●	●			
Others		substantia nigra	●	●			
		globus pallidus		● (internal)		● (external)	
		subthalamus		●		●	
		cerebral cortex	●				
		pyramidal tract	●	●			
		lower motor neurons	●	●			
		dorsal root ganglia	●	●			

pentanucleotide repeat expansion in an intronic region

●: neuronal loss

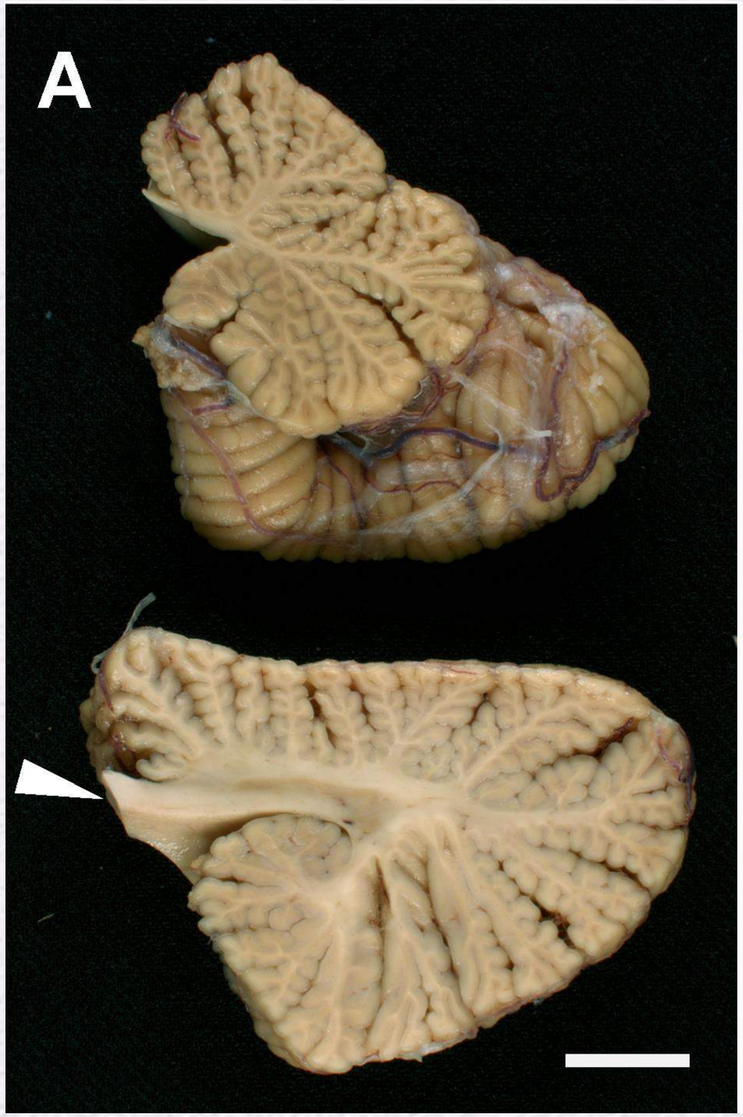
polyglutamine disorders

SCA6



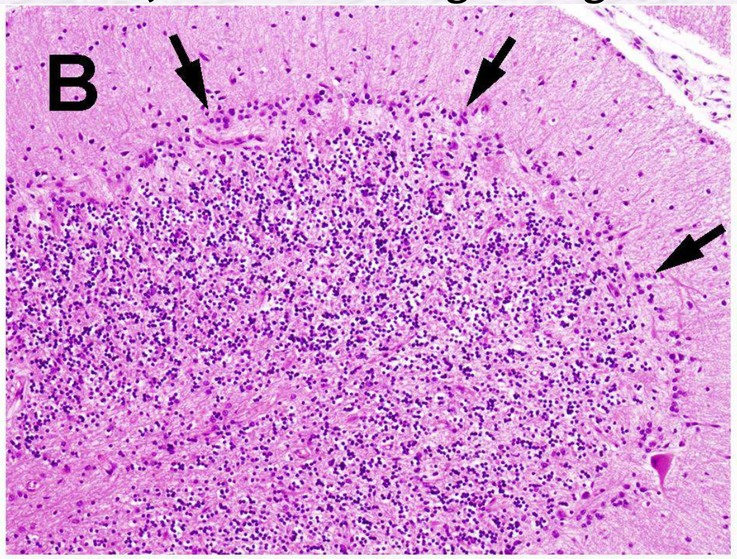
SCA6: cerebellum

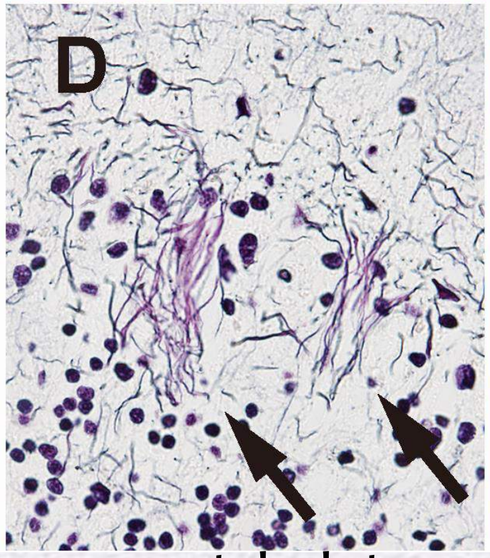
cbll cortical atrophy



preservation of the dentate n. & sup. cbll peduncle

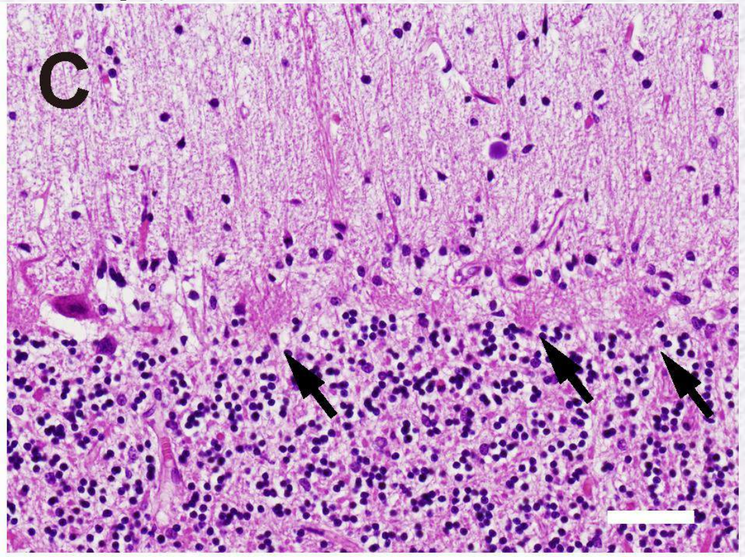
Purkinje cell loss & Bergmann gliosis

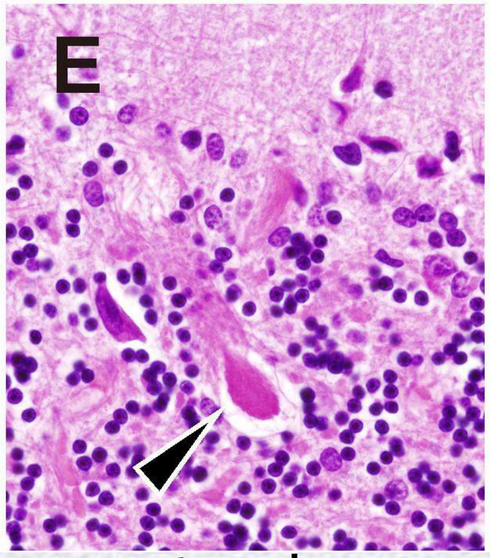




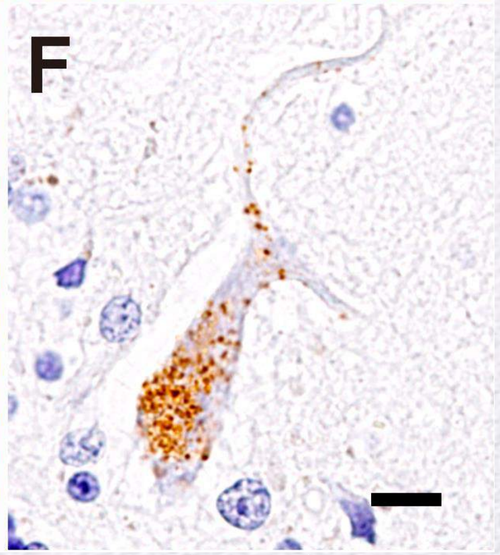
empty baskets
(Bodian silver stain)

empty baskets (processes of basket cells)





torpedo
(proximal axon swelling)

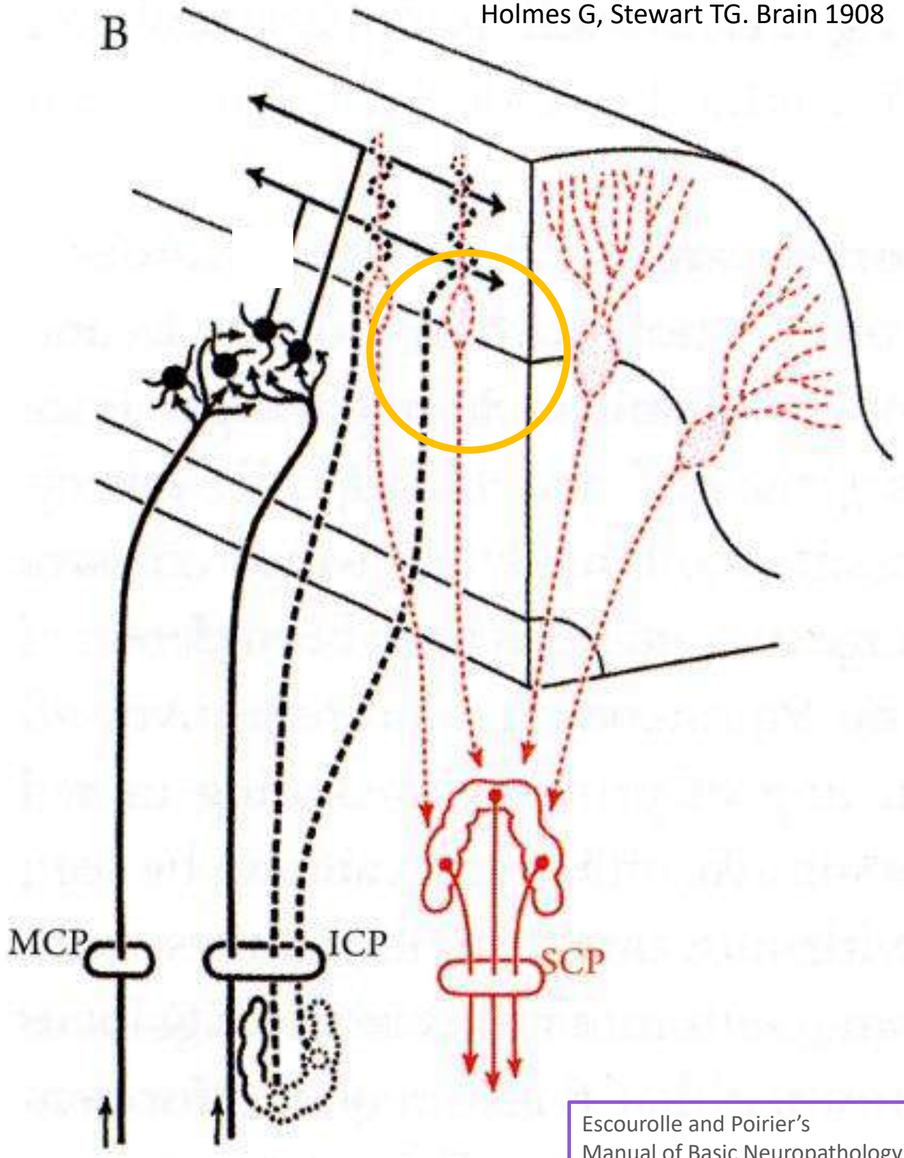


1C2 (polyQ): NCIs

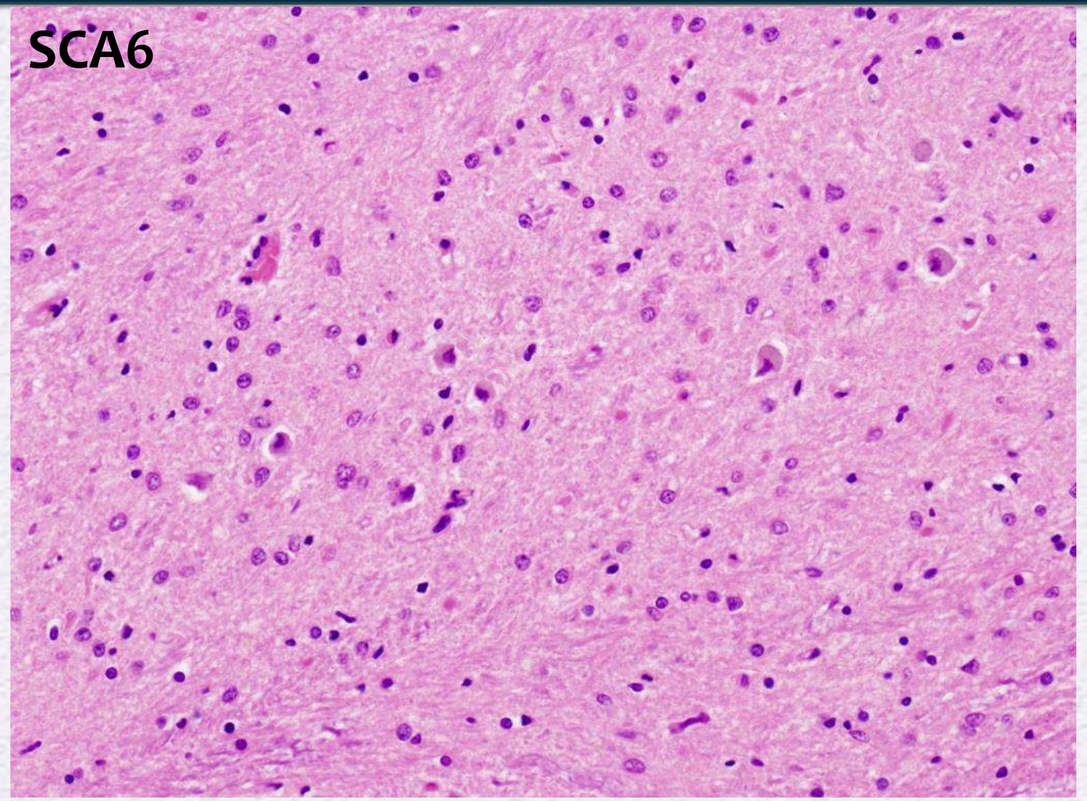
SCA6: inf. olivary n.

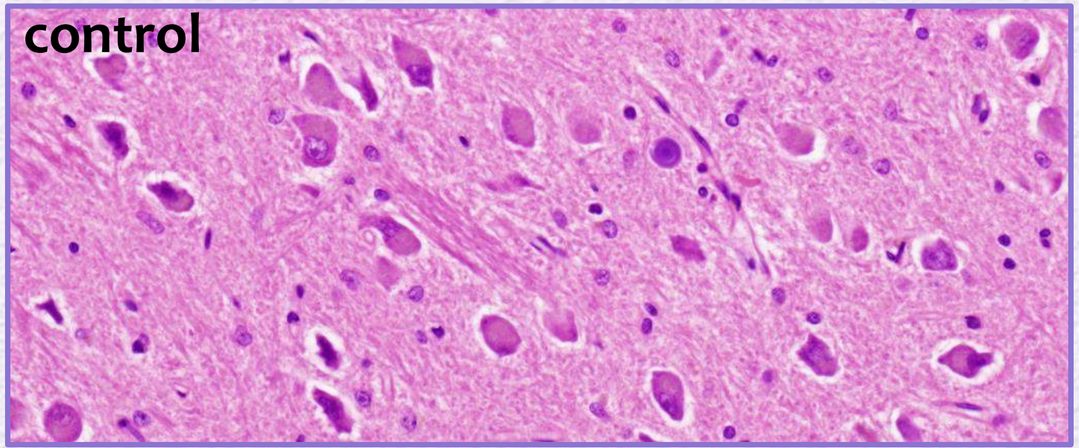
cerebello-olivary atrophy

Holmes G, Stewart TG. Brain 1908



Escourolle and Poirier's
Manual of Basic Neuropathology





SCA6

Pathology is simple!

Cortical cerebellar degeneration

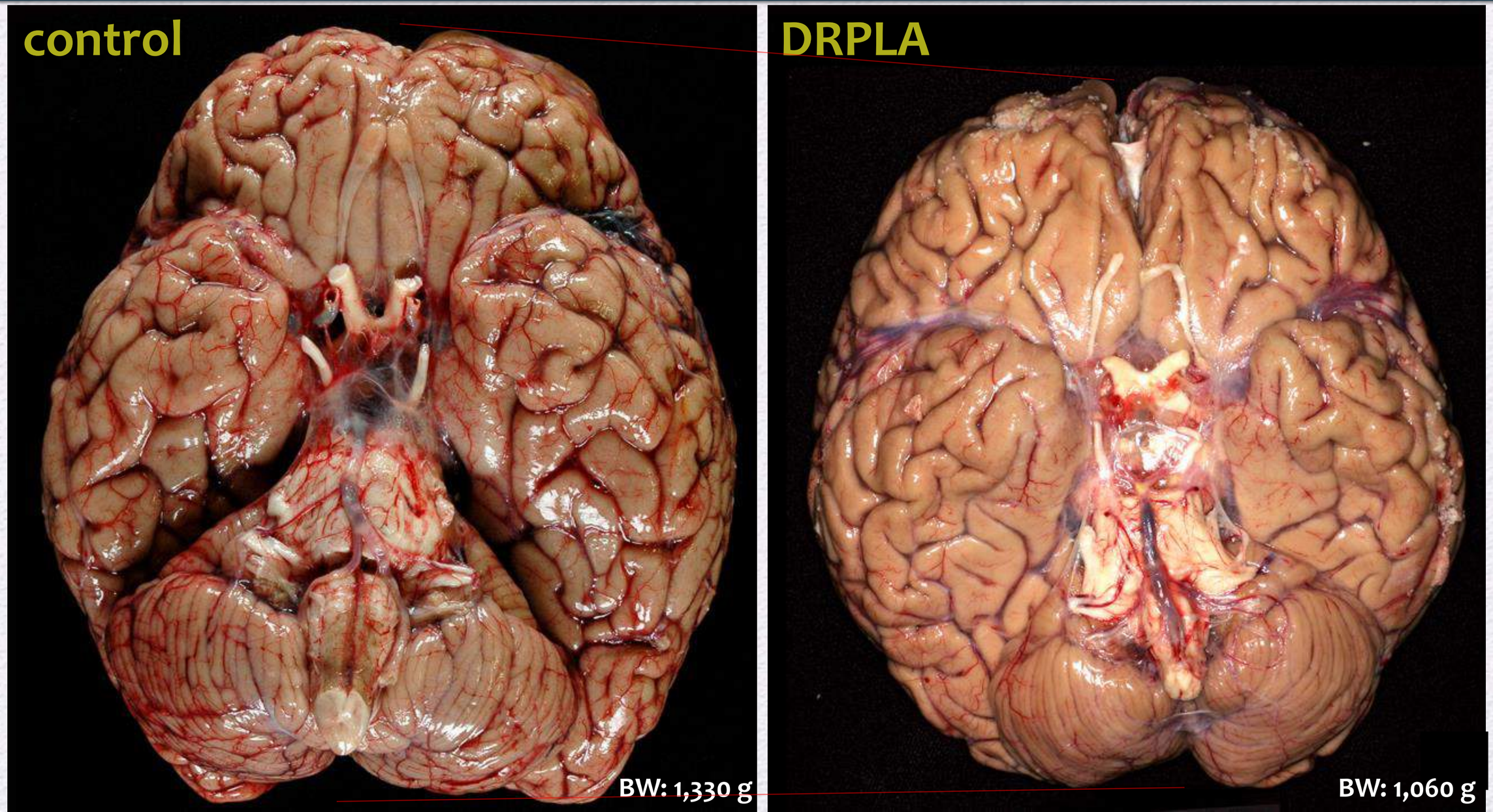
Purkinje cells > granule cells

Purkinje cells	1C2 (+) NCIs
	Torpedos: swelling of proximal axons
glial reaction	Bergmann glia proliferation
	Empty baskets

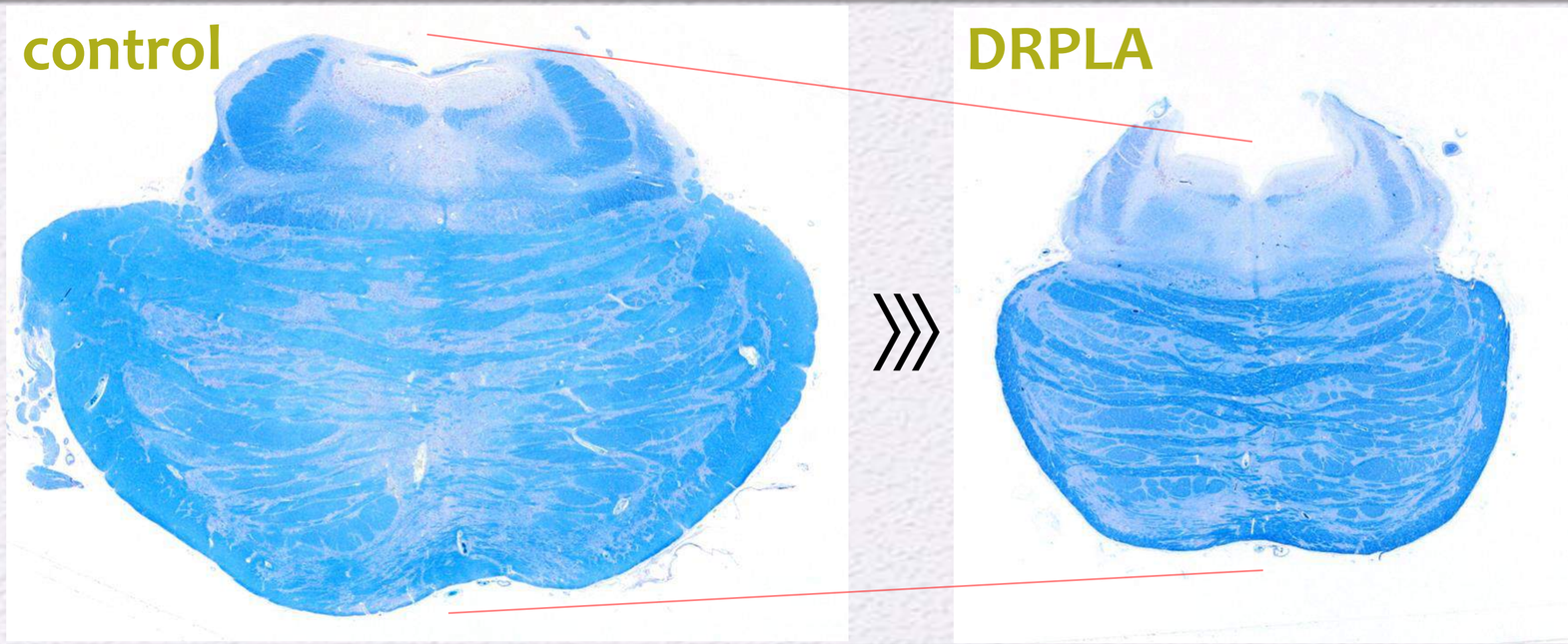
Inferior olivary nucleus neuronal loss

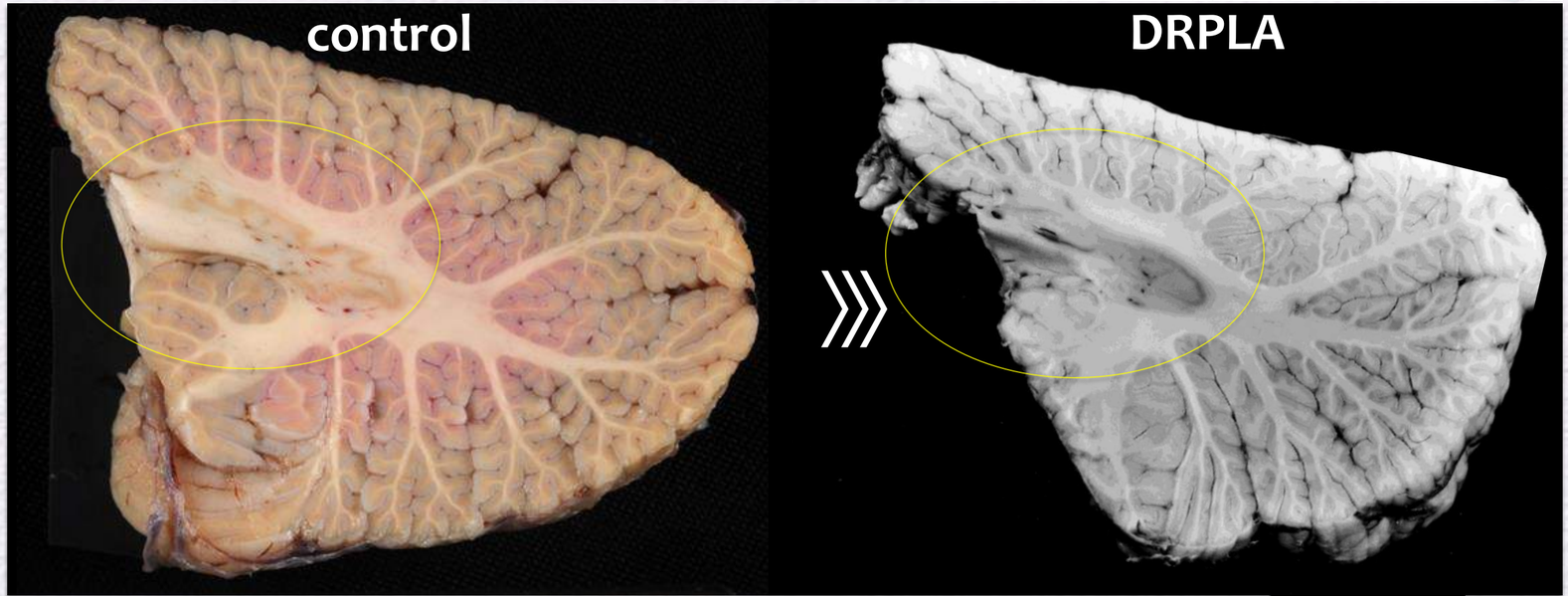
secondary retrograde degeneration

DRPLA: dentatorubral-pallidoluysian atrophy

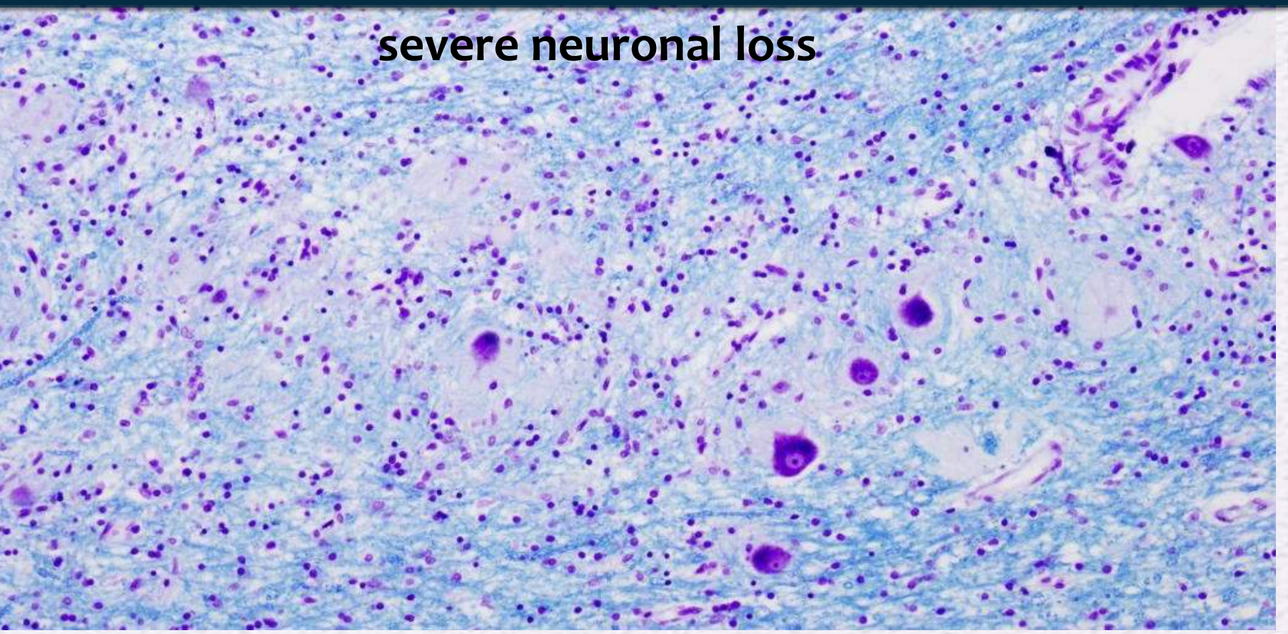


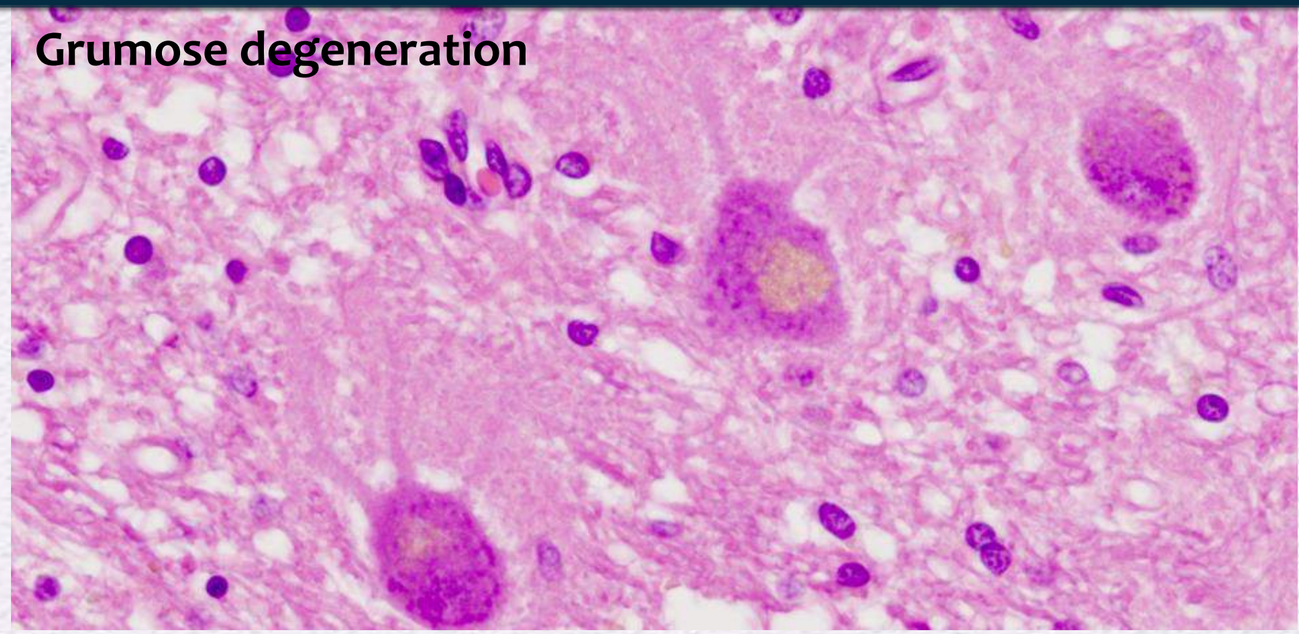
DRPLA: small, but well-proportioned brain

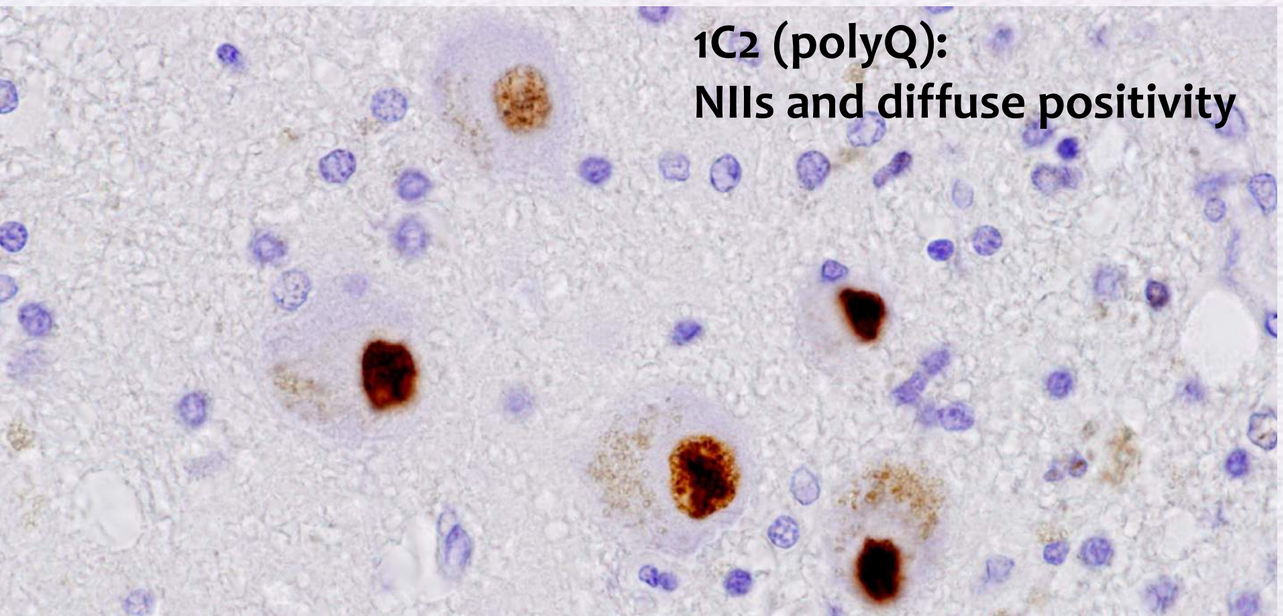


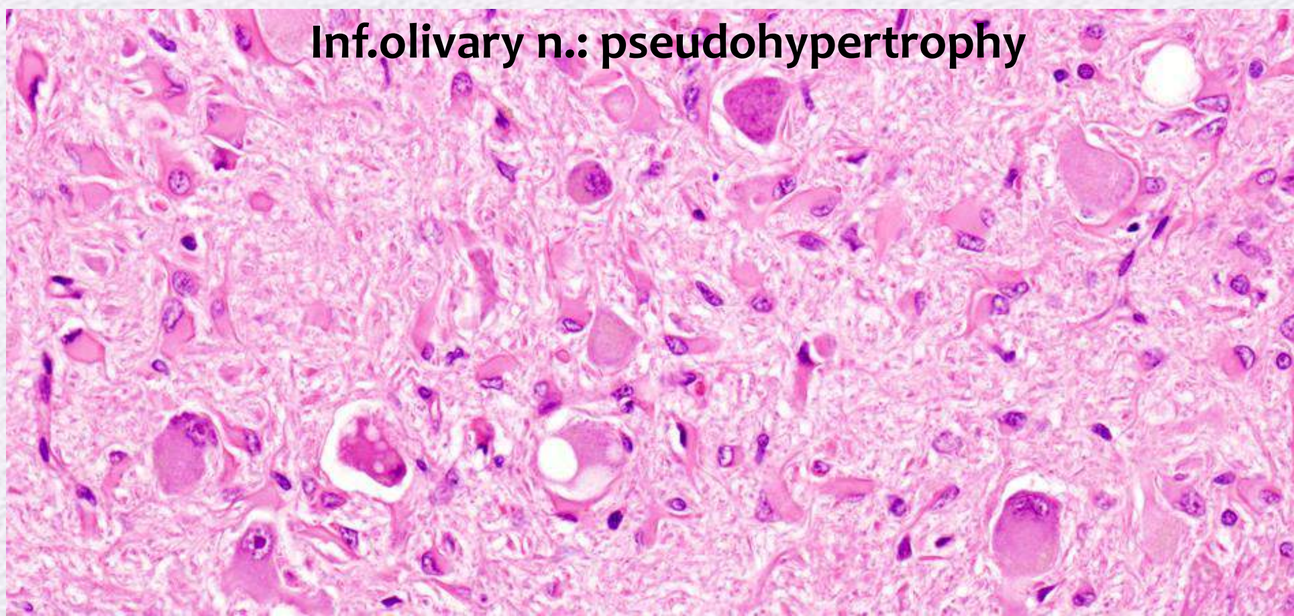


DRPLA: dentate nucleus







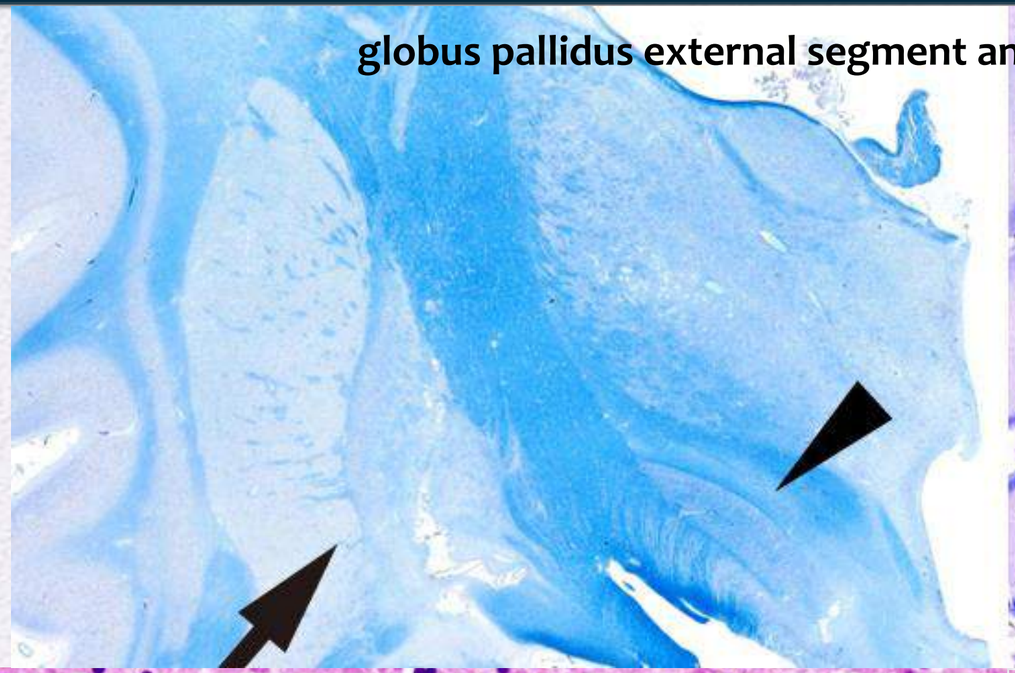


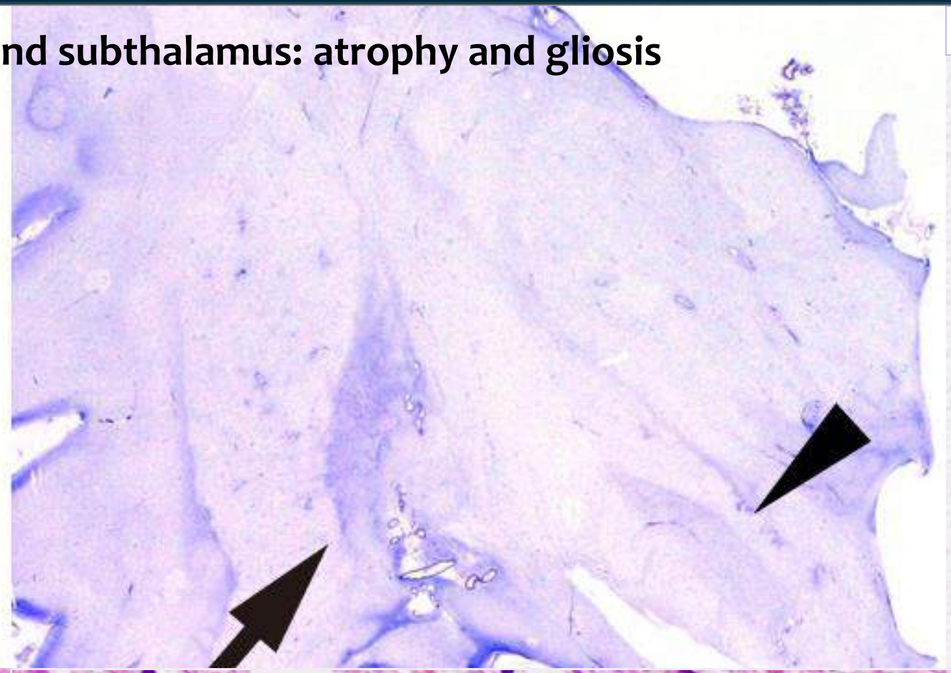
DRPLA: pallidoluysian

K-B stain for myelin

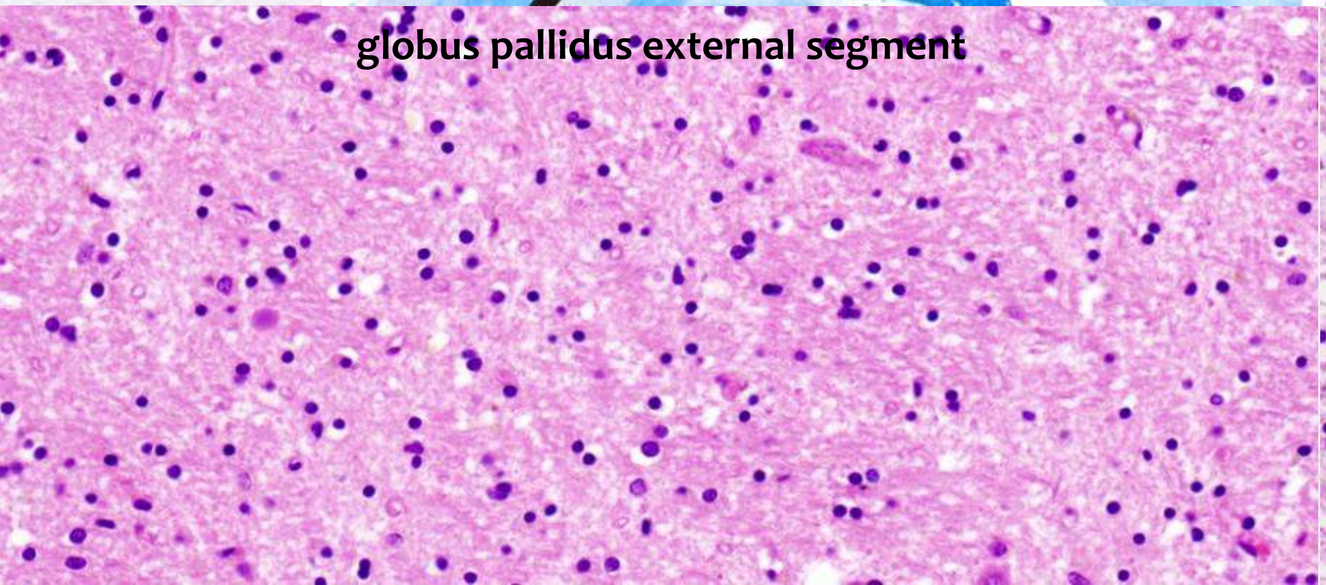
globus pallidus external segment and subthalamus: atrophy and gliosis

Holzer stain for gliosis

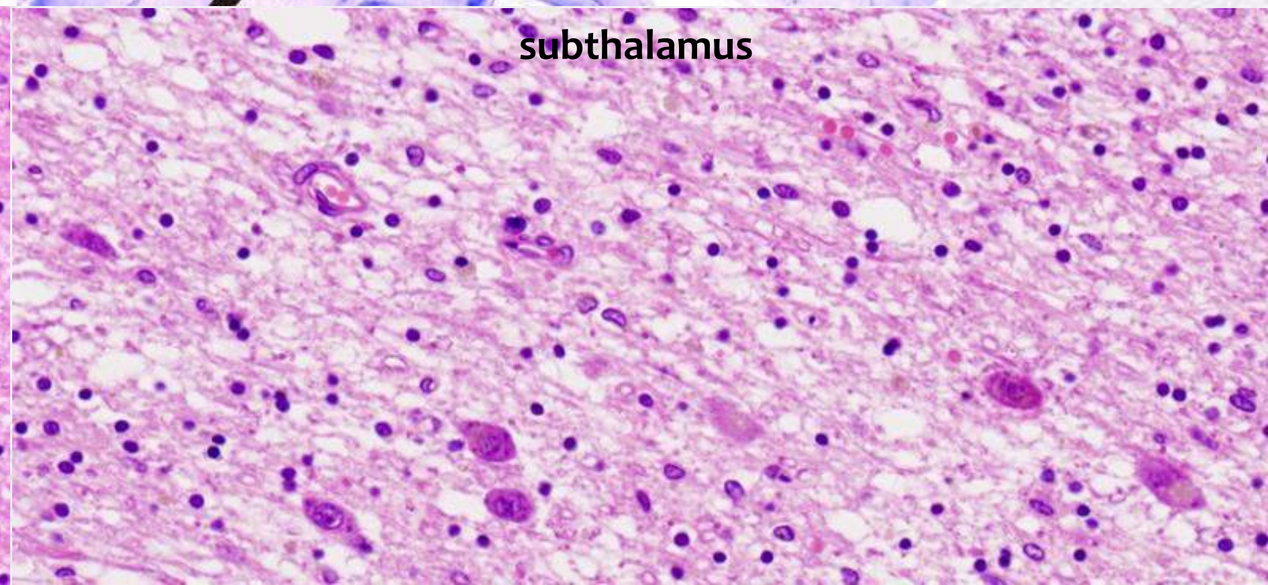




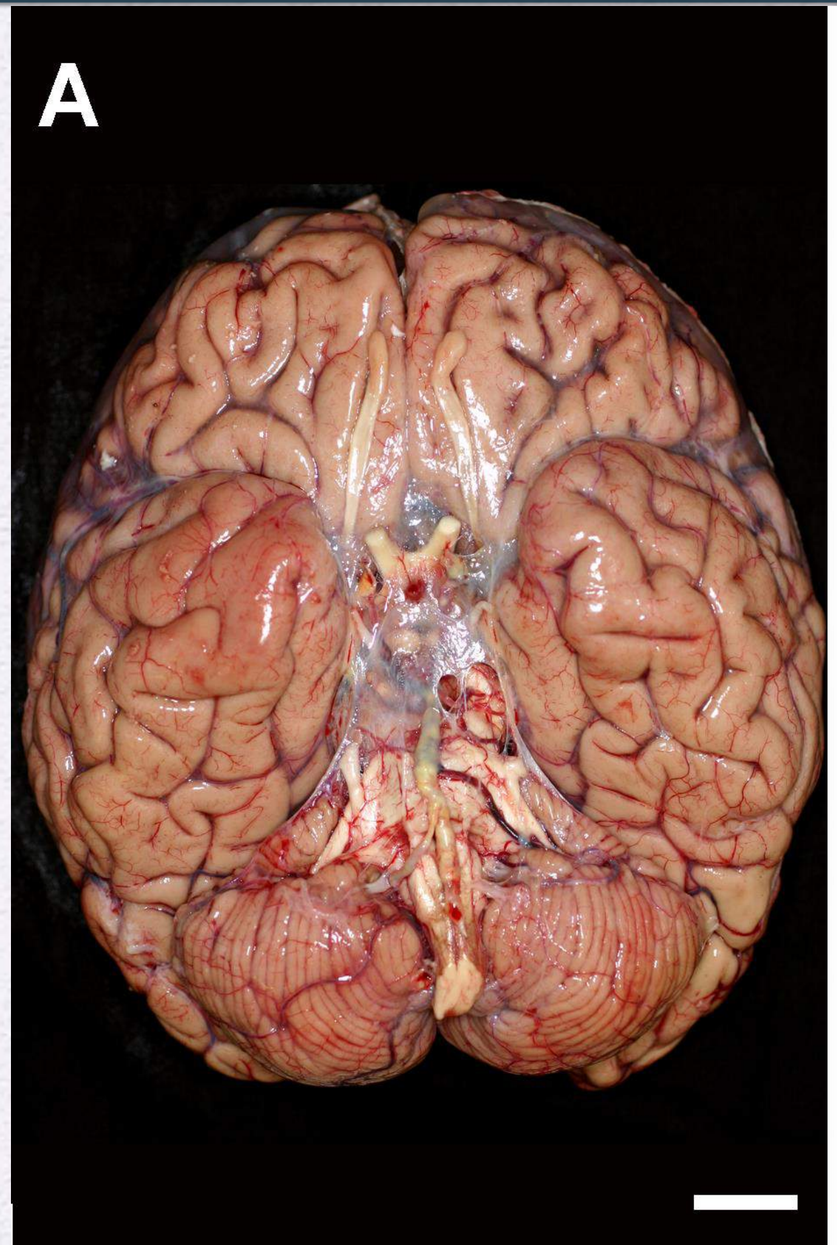
globus pallidus external segment

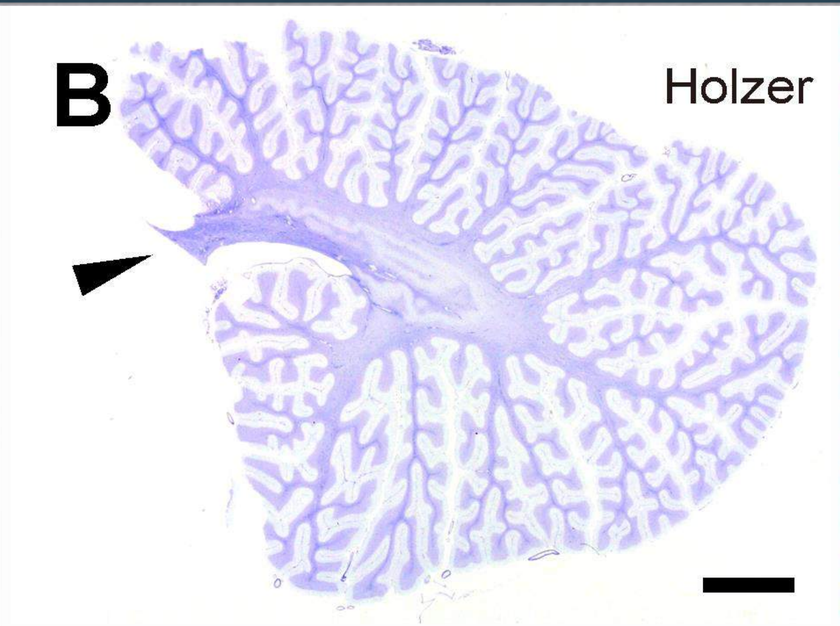


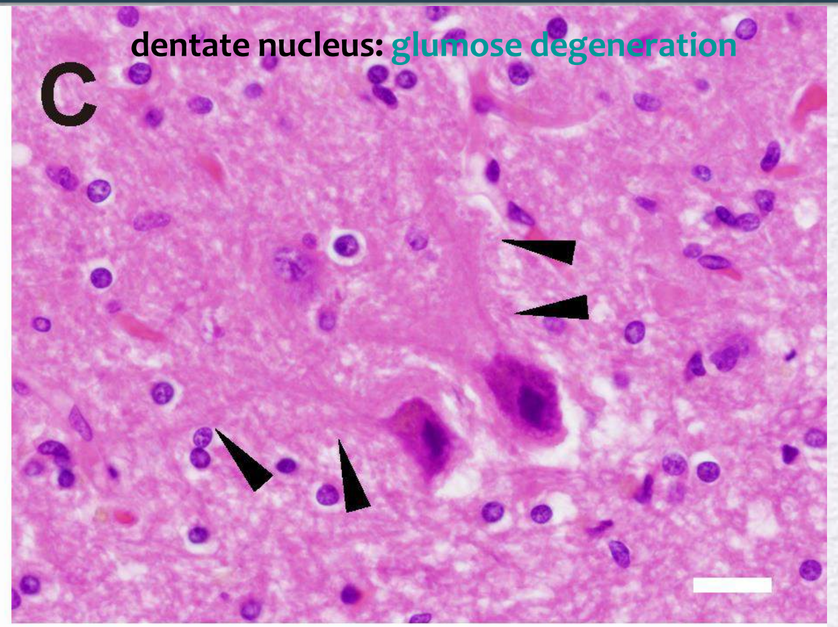
subthalamus

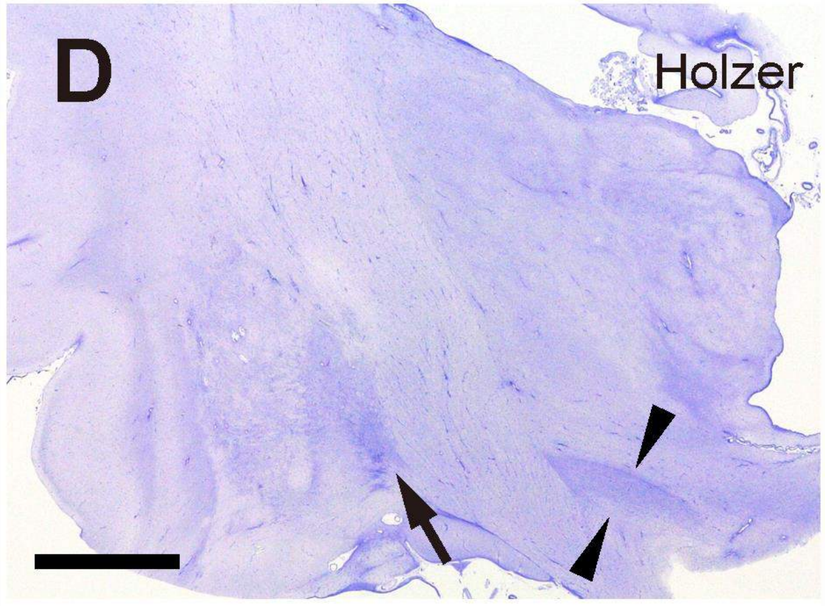


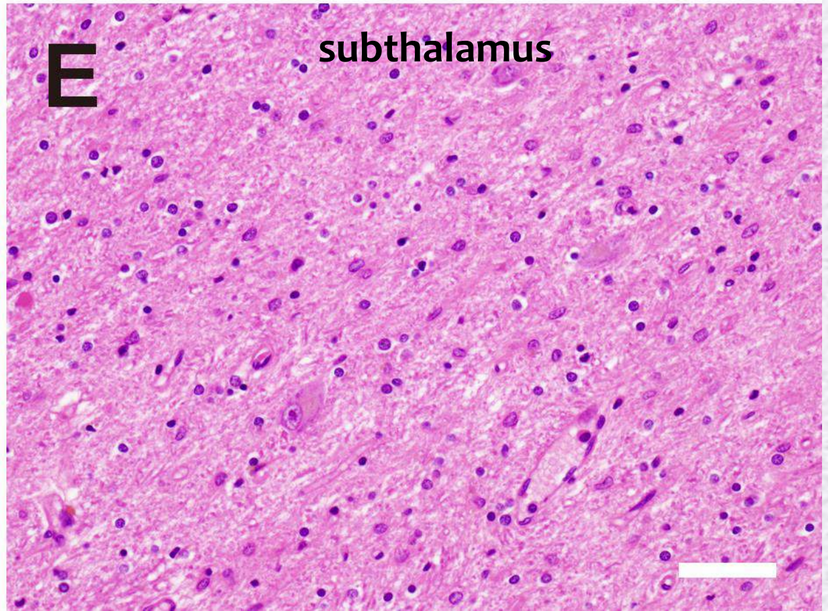
SCA3/MJD (Machado-Joseph disease)



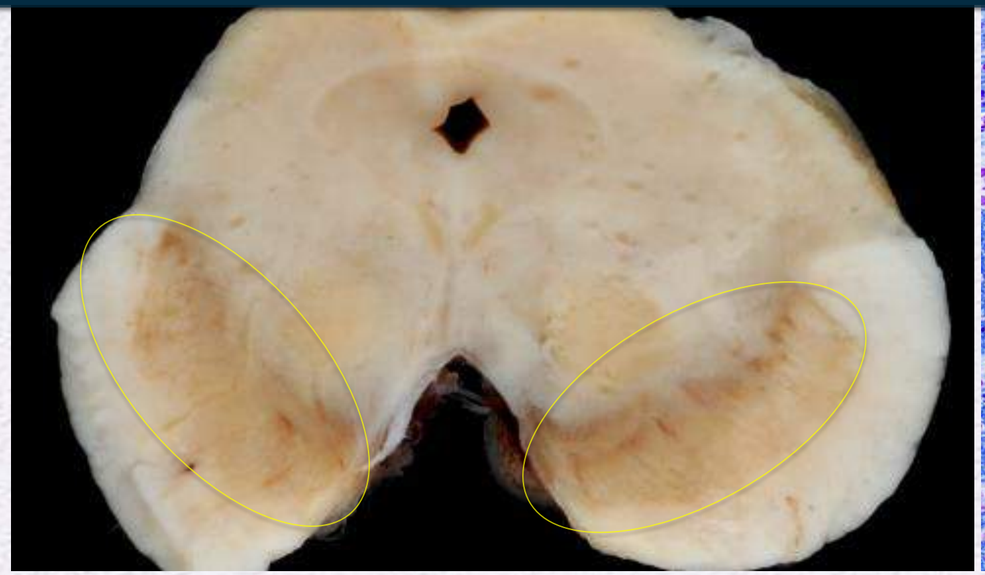


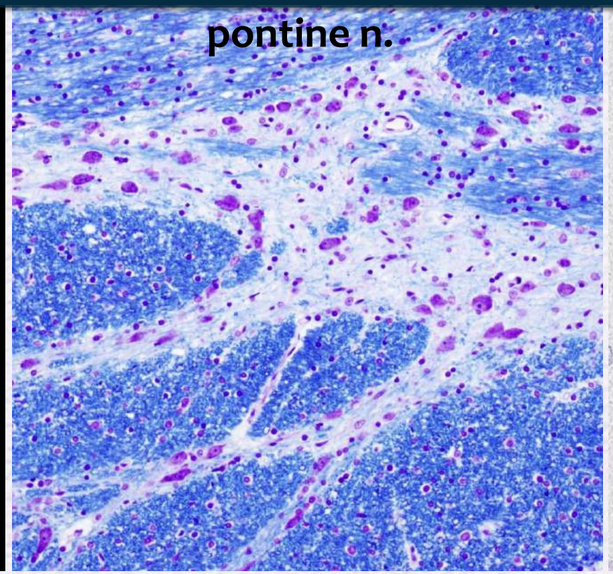


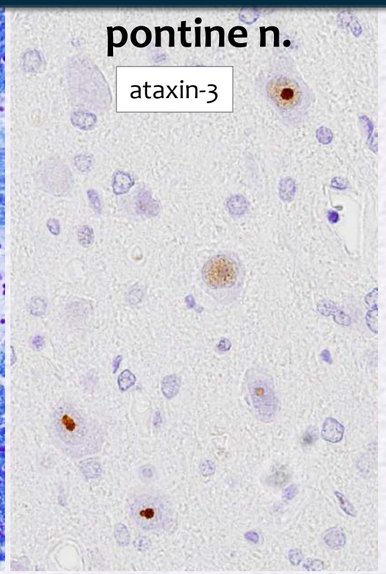


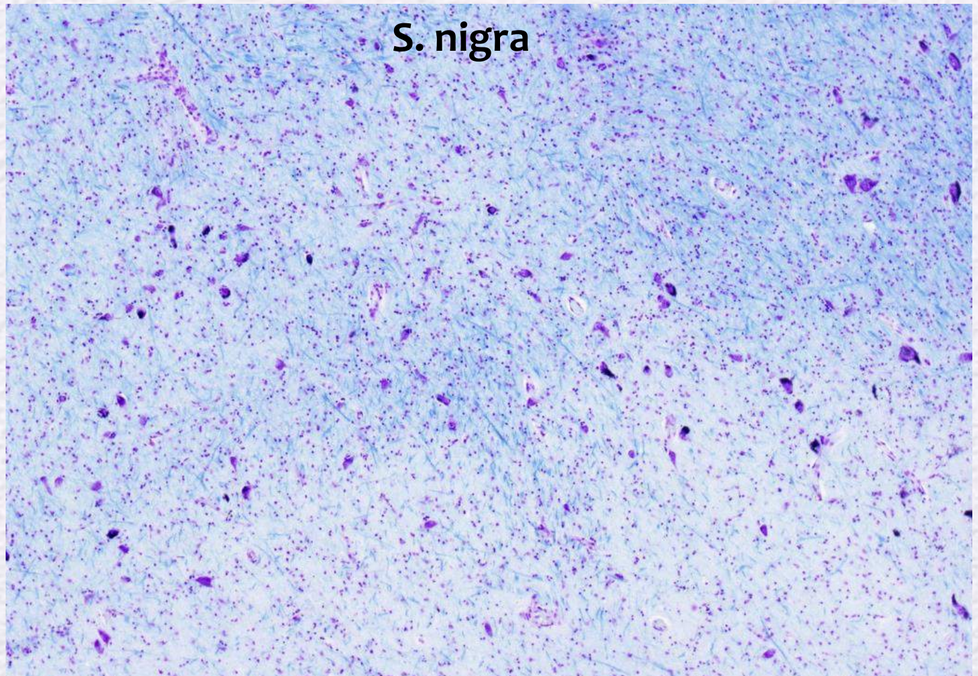


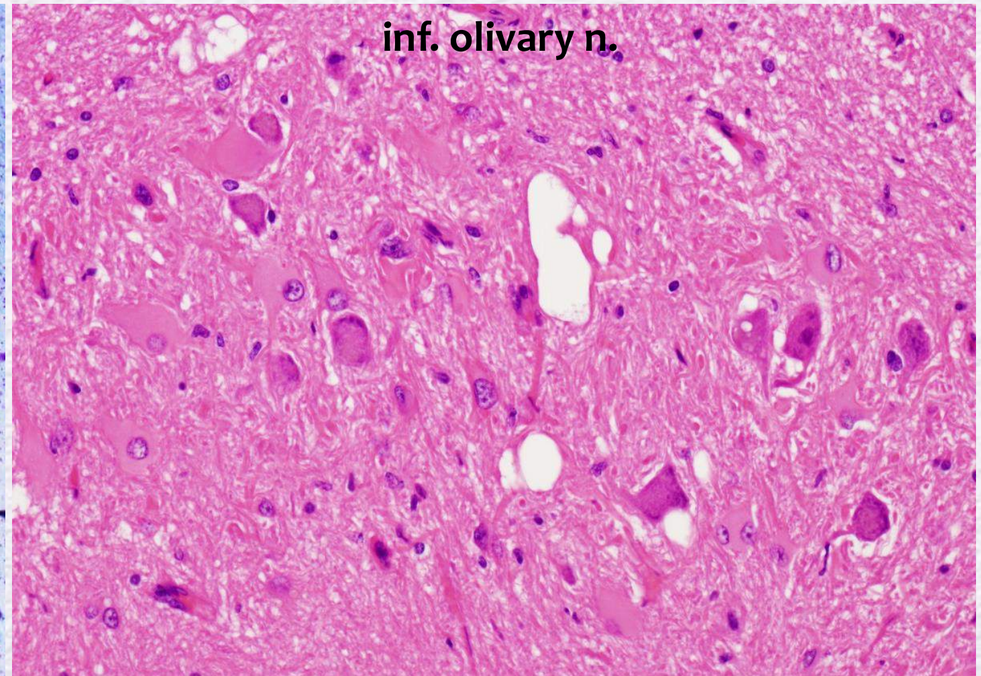
SCA3/MJD



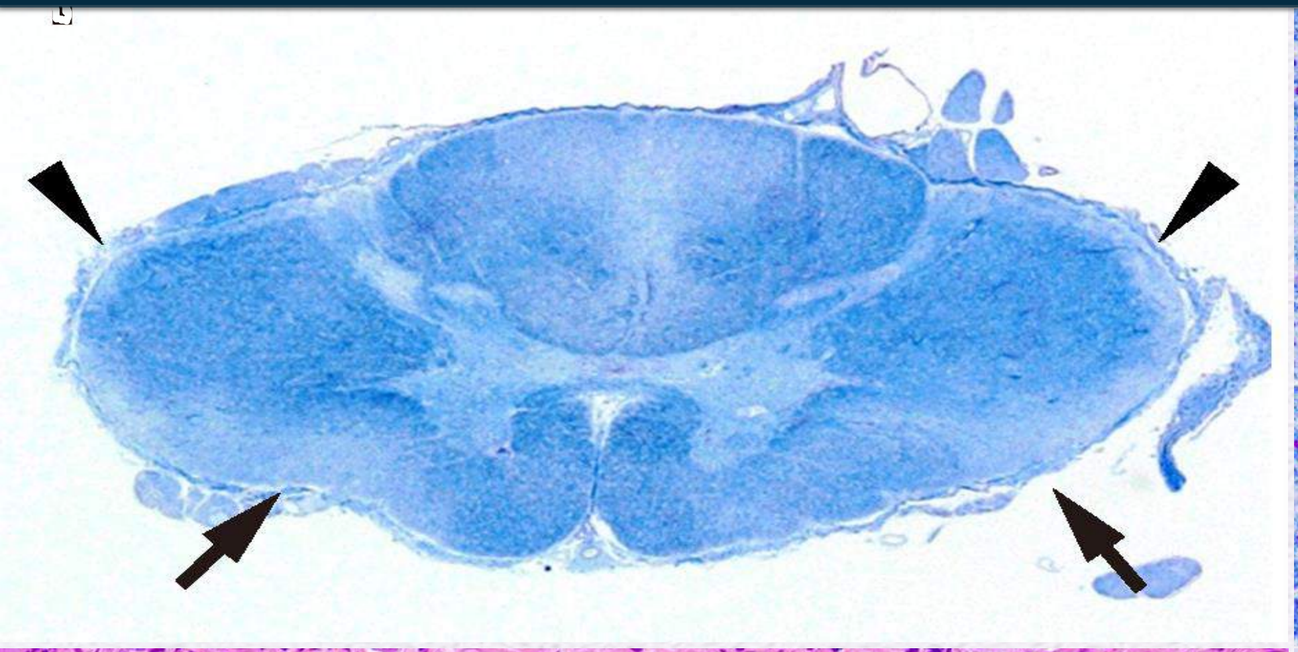


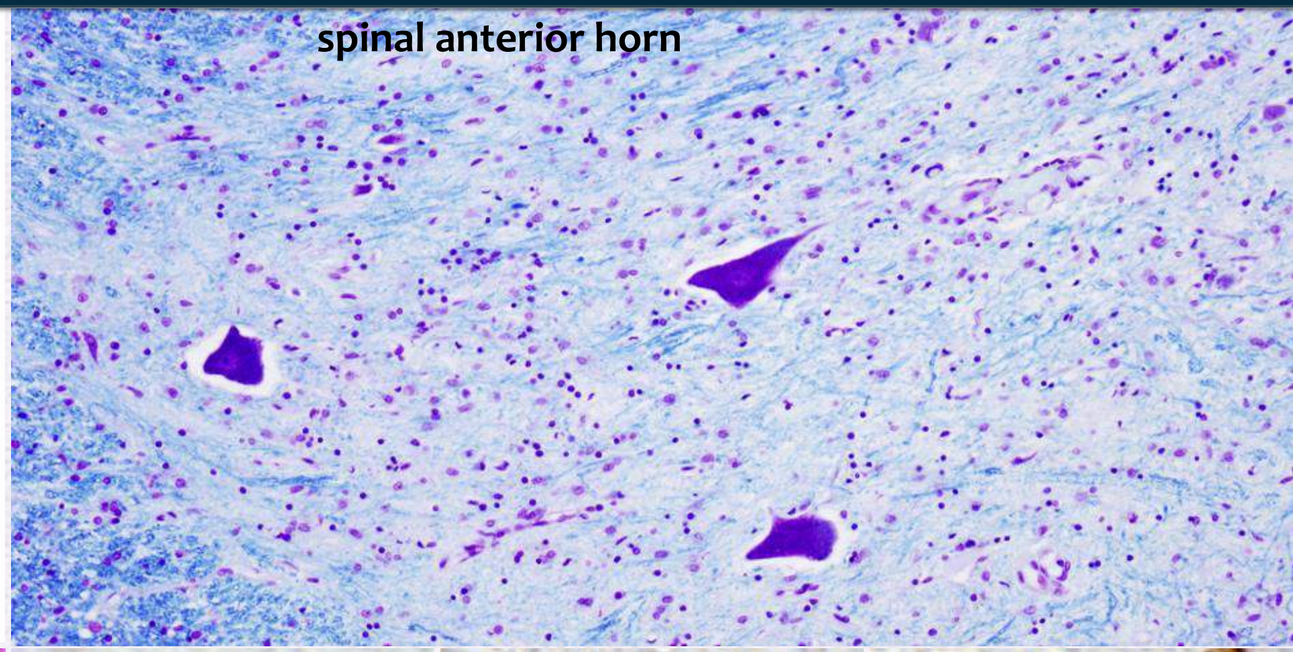


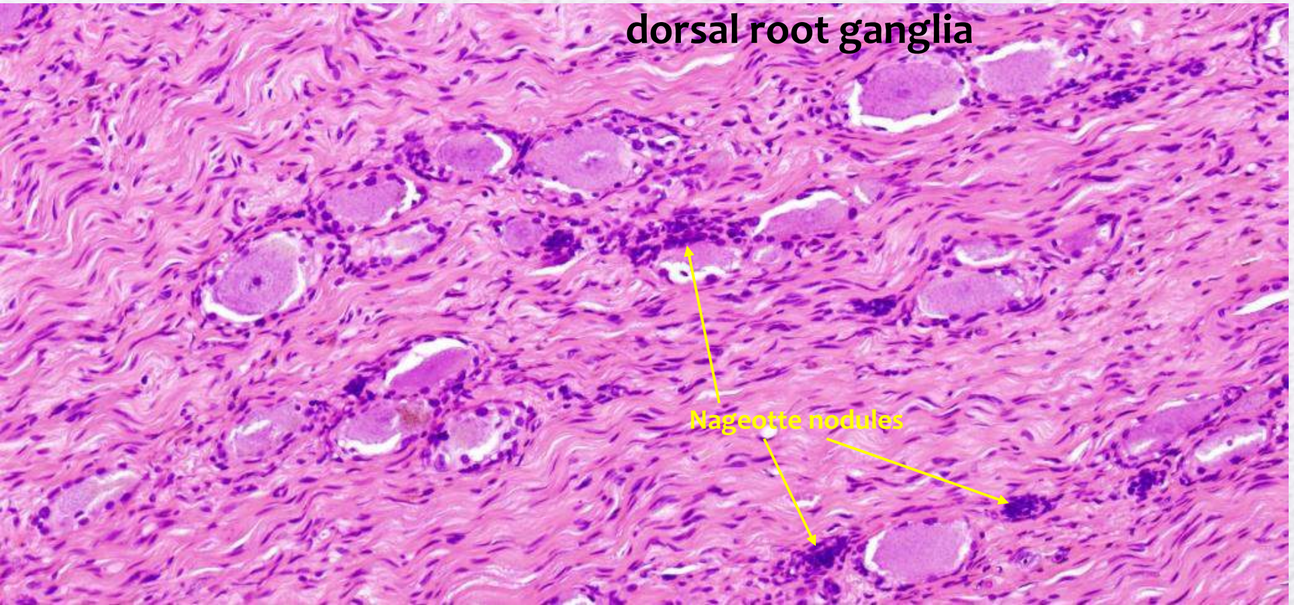


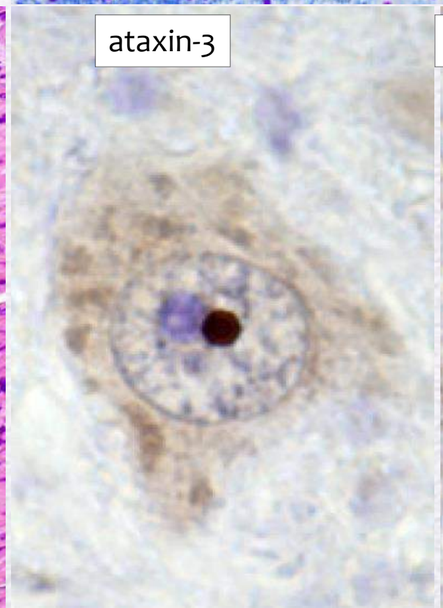


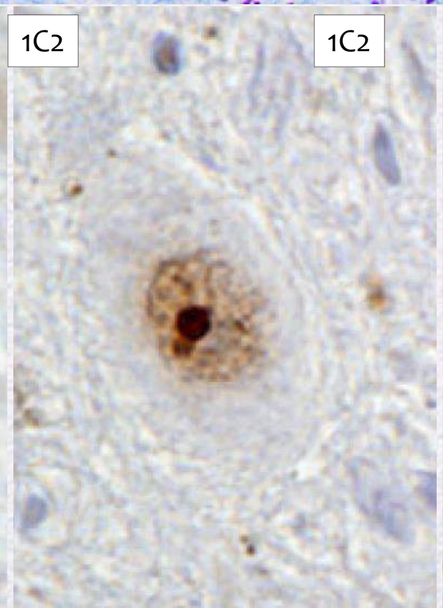
SCA3/MJD

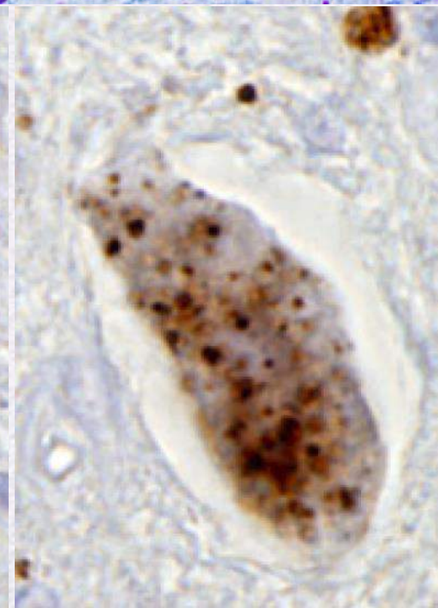



spinal anterior horn


dorsal root ganglia
Nageotte nodules

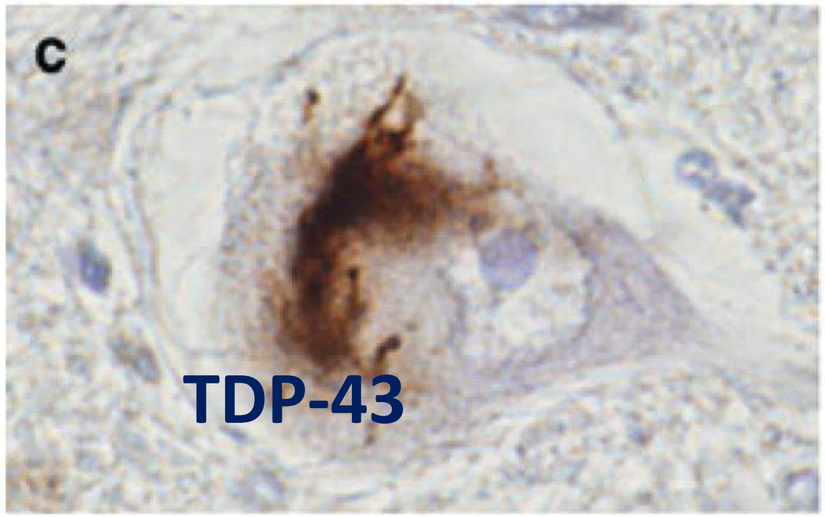

ataxin-3

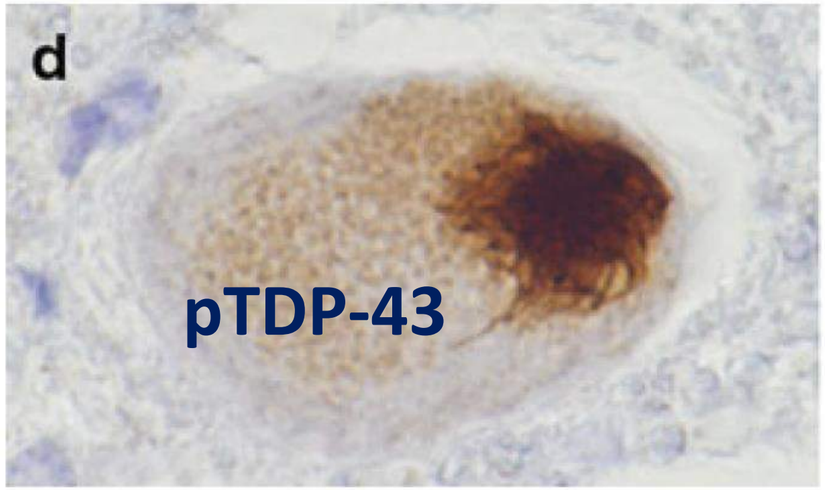

1C2

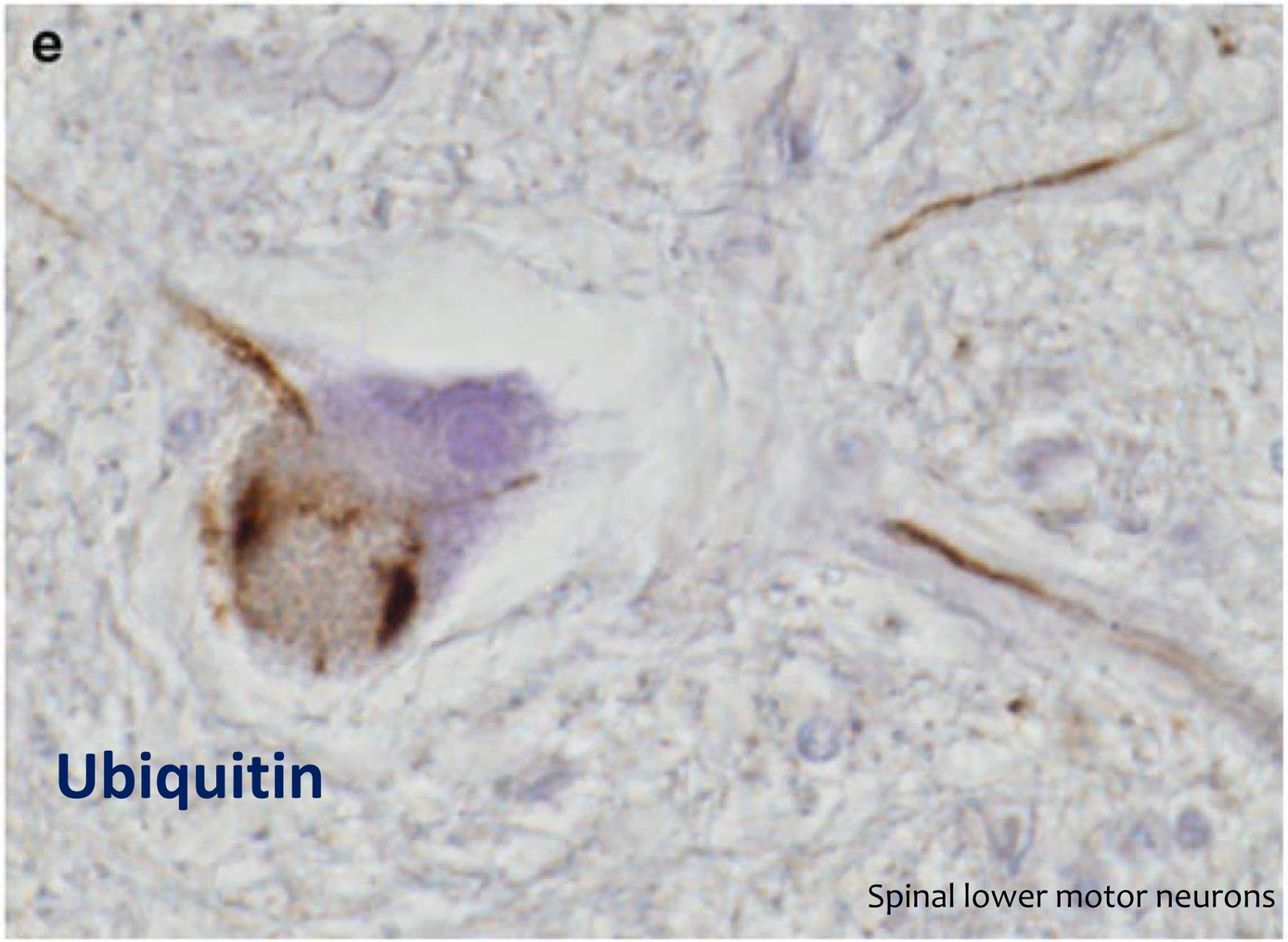

1C2

SCA3/MJD

TDP-43 inclusions in the cytoplasm and processes

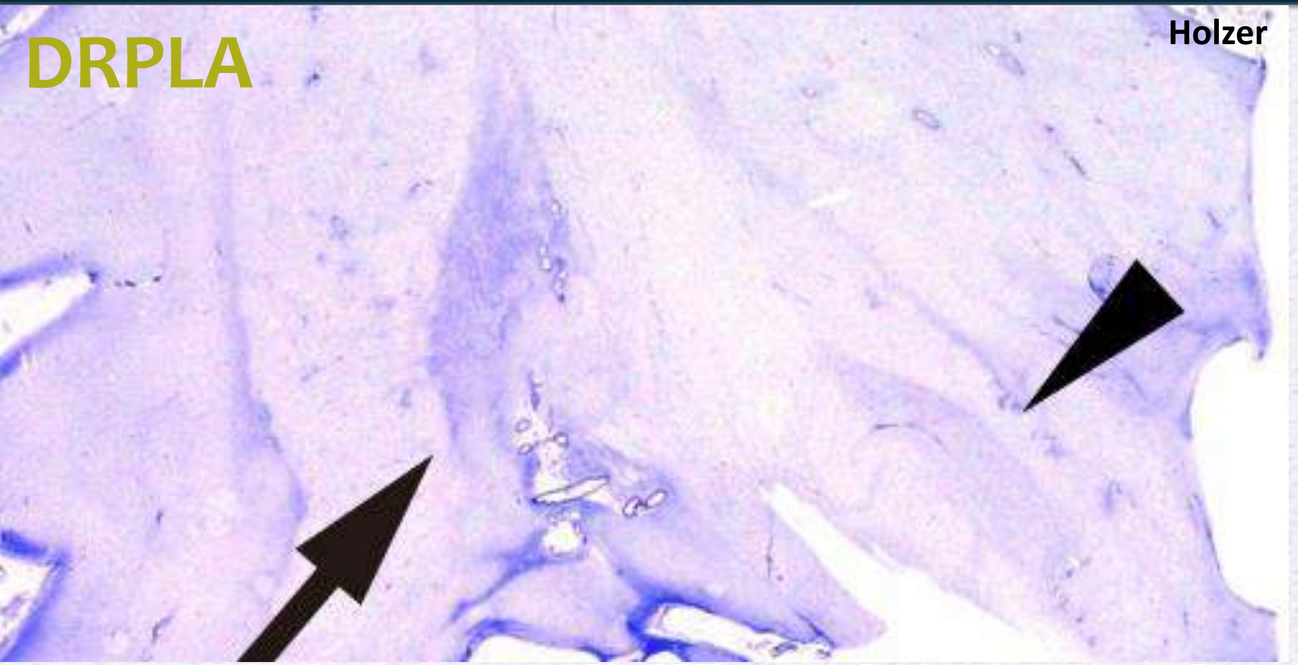


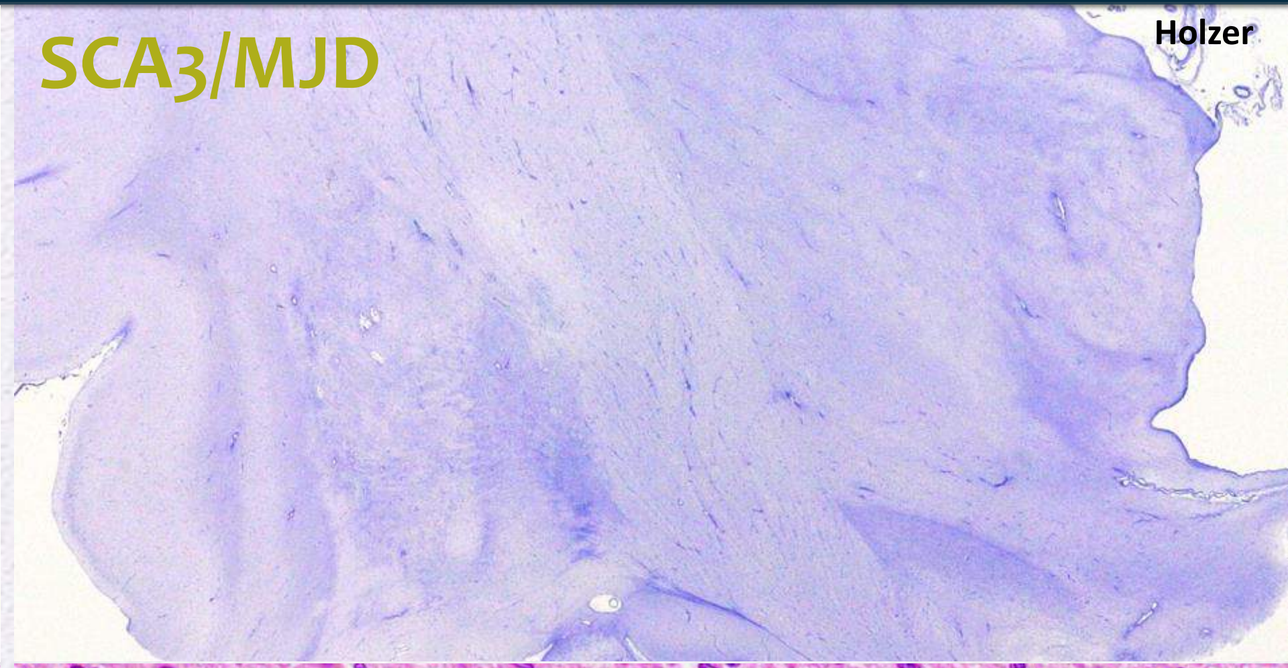


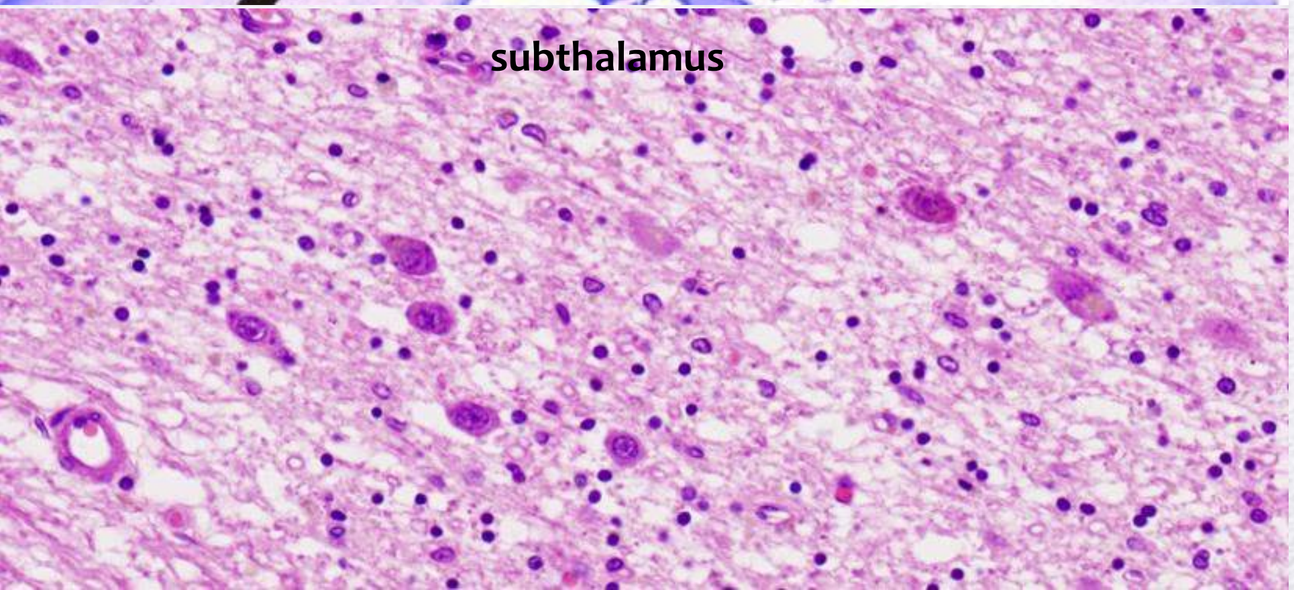


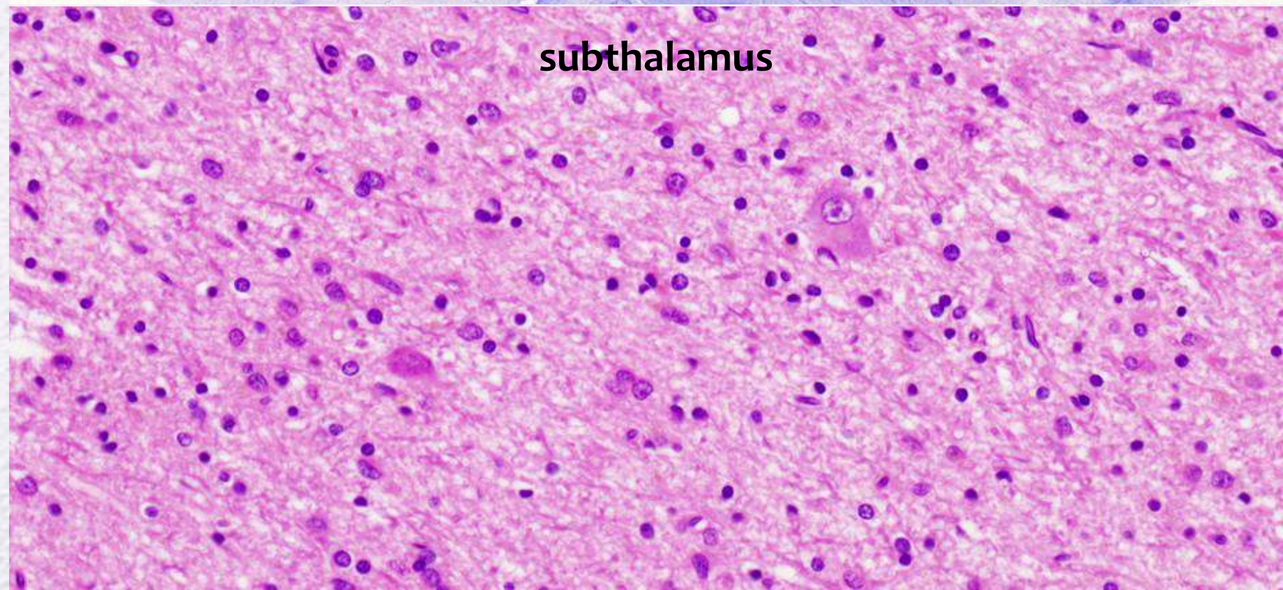
Tan CF, et al. Acta Neuropathol 2009; 118: 553-560.
Shimizu H, et al. Acta Neuropathol 2010; 120: 439-448.

DRPLA vs SCA3/MJD









DRPLA vs SCA3/MJD

Multi-system degeneration !

DRPLA

Cbll dentate n. > red n.
grumose degeneration
pseudohypertrophy of the inf. olivary n.

Globus pallidus（ext. seg. **>** int. seg.）
> subthalamus

1C2 (+) inclusions
diffuse nuclear staining
widespread, including the cbr cortex

vs

SCA3/MJD

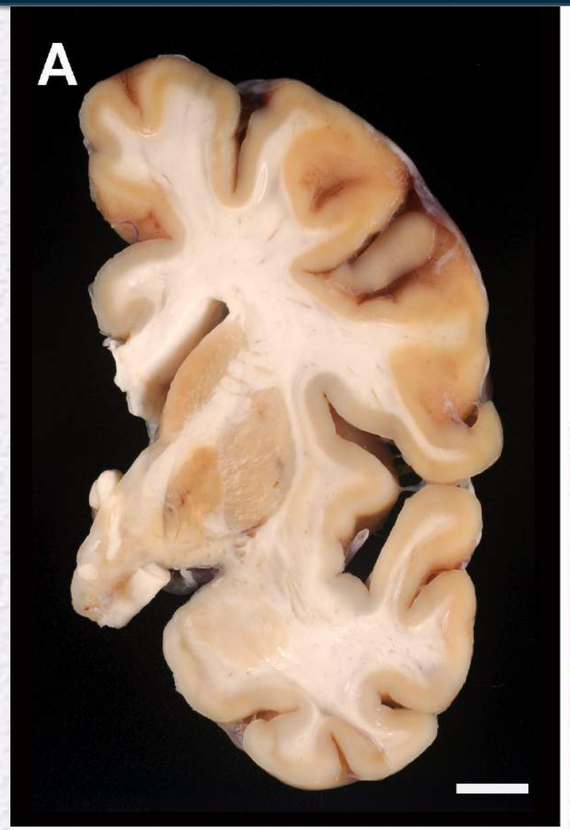
Cbll dentate n. > red n.
grumose degeneration
pseudohypertrophy of the inf. olivary n.
cerebellar “afferent” tracts
pontine n., Clarke column

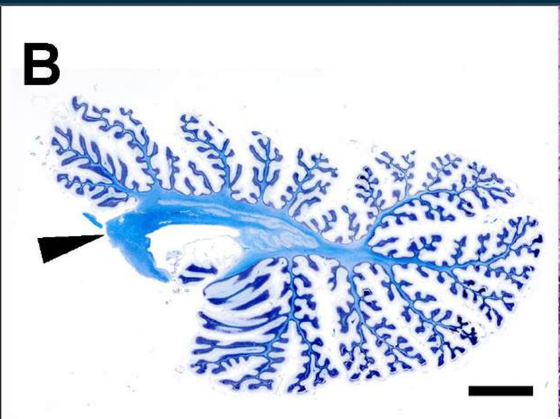
Globus pallidus（ext. seg. **<** int. seg.）
< subthalamus
S. nigra
pyramidal tract, lower motor neurons
dorsal root ganglia
cerebral cortical neurons

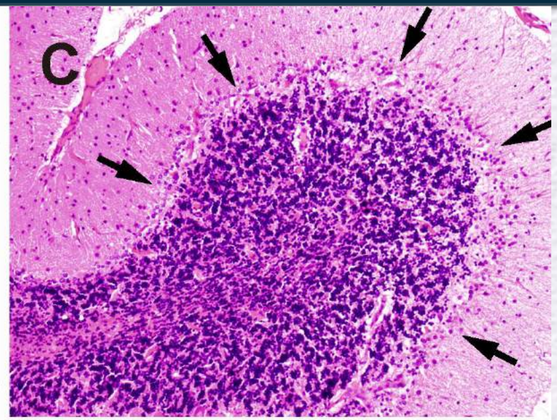
1C2 (+) inclusions
NIIs, diffuse nuclear staining
widespread, including the cbr cortex

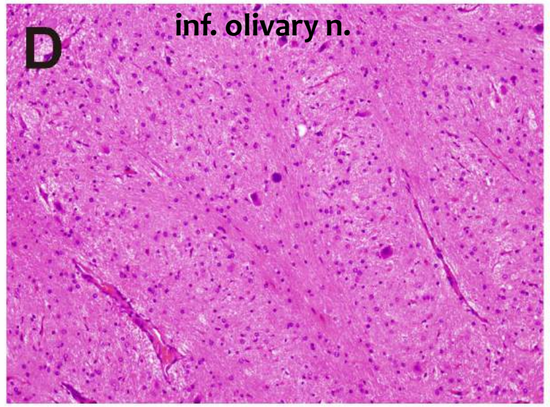
SCA2

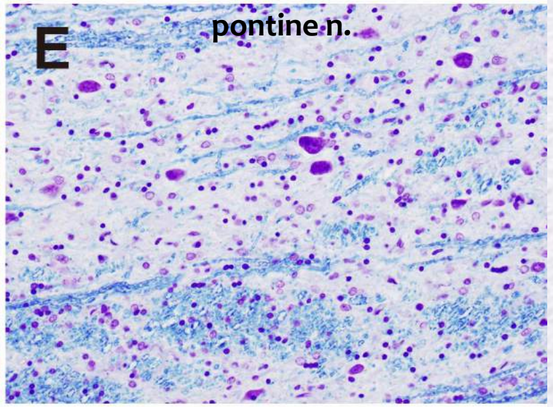
- Widespread atrophy in the cerebrum, cerebellum, brain stem, spinal cord, and peripheral nerves.
- Purkinje cell loss, but the superior cerebellar peduncle is preserved.
- Degeneration in the inferior olivary nucleus, pontine nucleus, S. nigra, brain stem motor nuclei, and spinal anterior horn cells is a feature.
- 1C2-positive neuronal cytoplasmic and nuclear inclusions.
- pTDP-43ipositive cytoplasmic inclusions in neurons and glia.

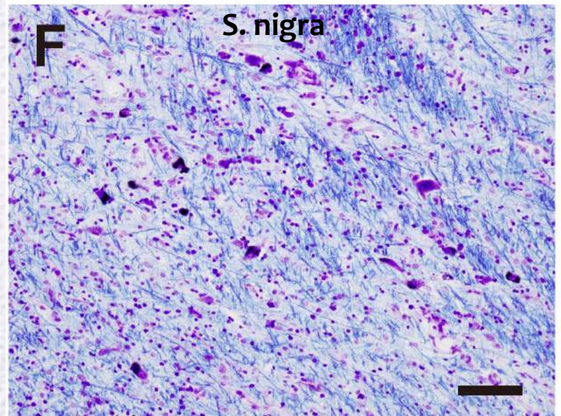


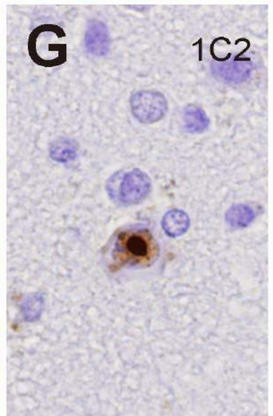


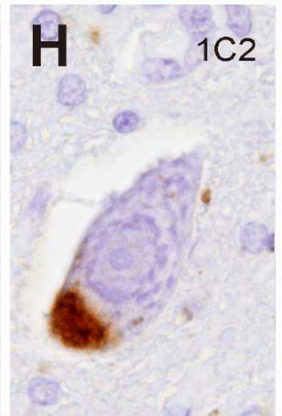


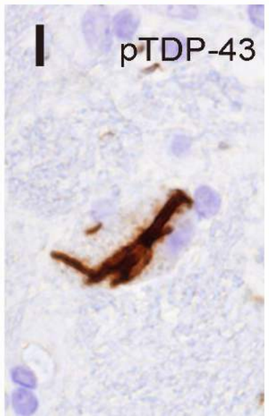


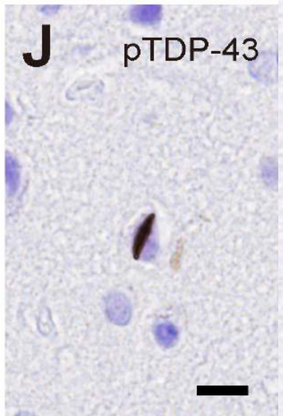




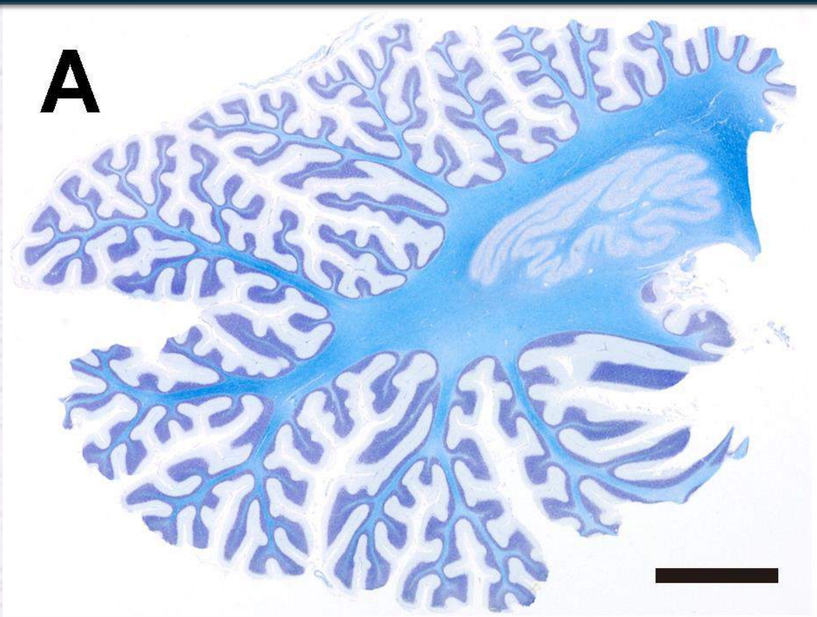


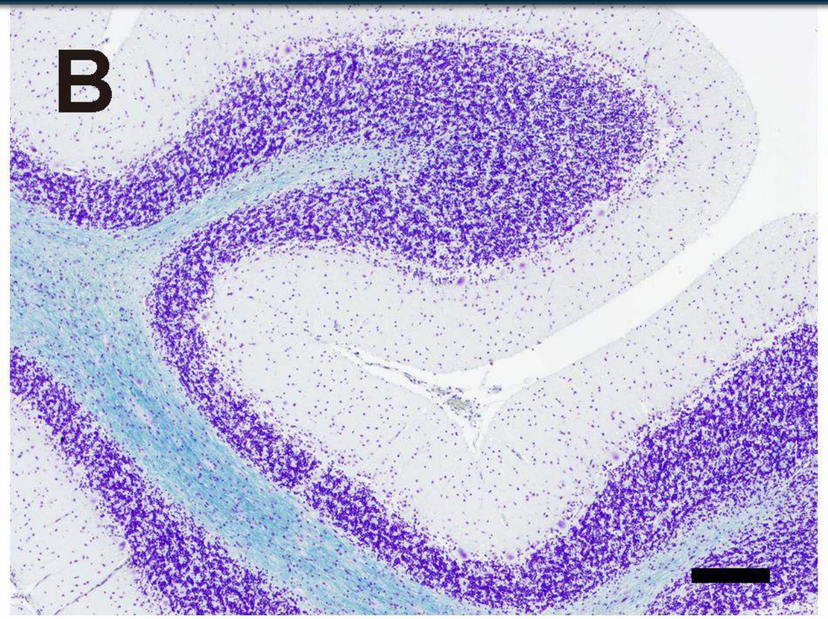


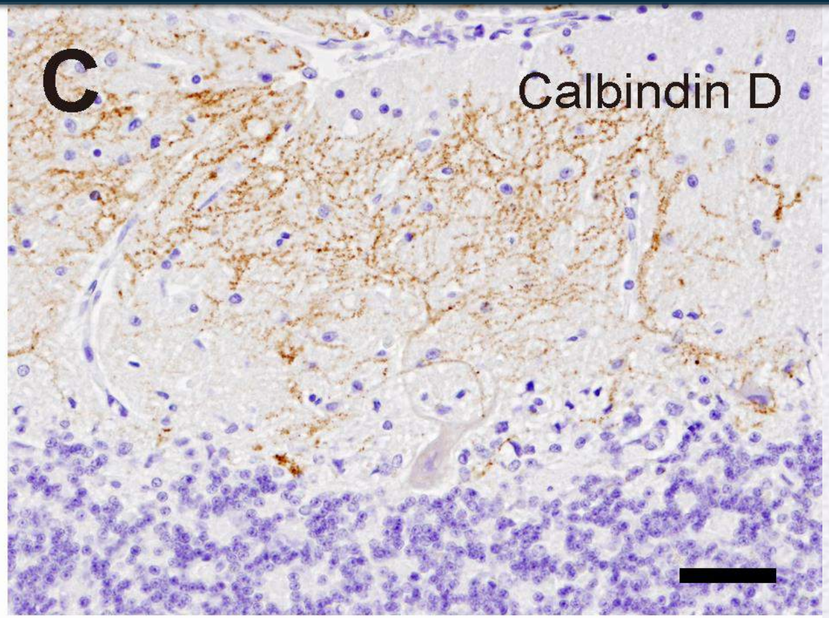


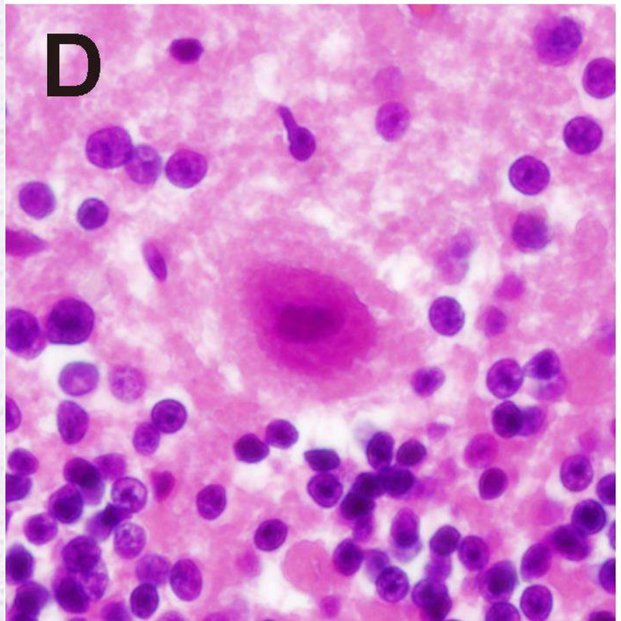


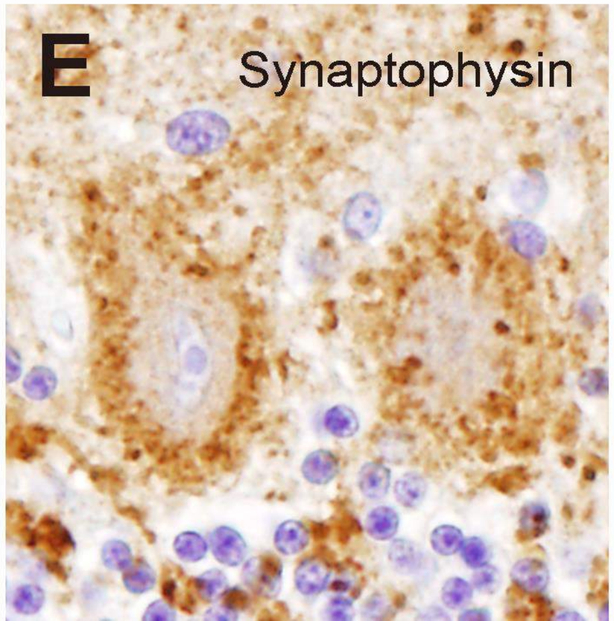
SCA31

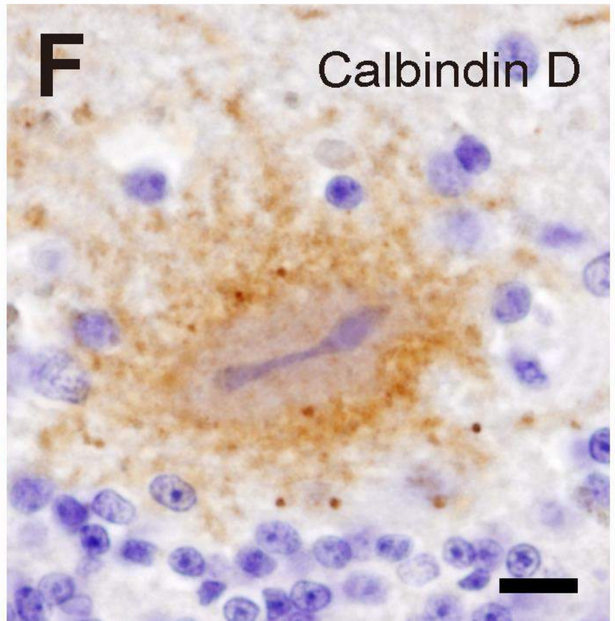


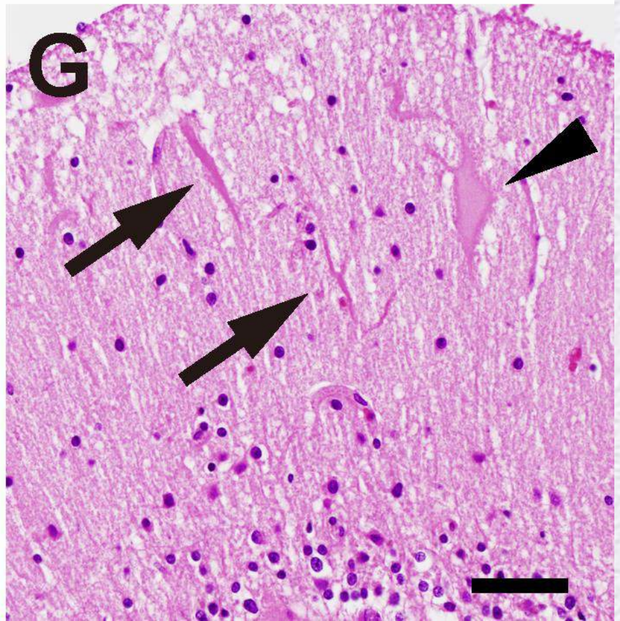












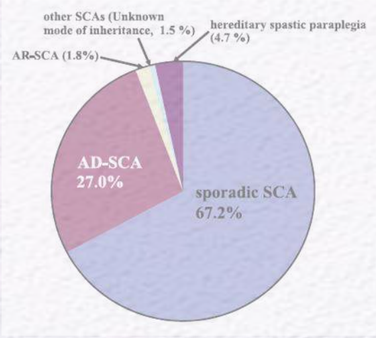
Presentation outline

1 pathologic features of a representative α-synucleinopathy
MSA – Sporadic disorder

2 for a better understanding of systemic degeneration ....
Cerebellum: anatomy

3 pathologic features of spinocerebellar ataxias
Autosomal Dominant disorders
SCA6, DRPLA, SCA3/MJD, SCA2, SCA31

4 pathologic features of spinocerebellar ataxias
Autosomal Recessive disorders
ARCA-*CHP1*, *SYNE1*-ataxia, SCA17-DI



All the presenting cases were experienced at the Brain Res Inst, Niigata Univ, Japan

ARCA-*CHP1*

Patient 1 (Pt 1)*

30 y.o. Drunken gait and slurred speech
52 y.o. Cognitive impairment followed by depression, delusion and restless
55 y.o. Cognitive impairment (WAIS-R: IQ 34), slurred speech, areflexia, adiadochokinesis and ataxia Romberg sign + and hearing loss. **SCD dx**.
62 y.o. Nystagmus, bulbar palsy, bilateral extensor plantar reflex and dysuria appeared
65 y.o. Bedridden
66 y.o. Died from repeated melena (autopsy)

Patient 2 (Pt 2)*

Mild mental retardation from childhood
56 y.o. Deteriorated gait disturbance
Cognitive decline (HDS-R: 17/30)
61 y.o. Nystagmus, hearing loss, slurred speech, extensor plantar reflex, adiadochokinesis and ataxic gait. Cerebellar atrophy on CT. **SCD dx**.
66 y.o. Dysuria
69 y.o. Worsened cognitive function (WAIS-R: IQ 30)
76 y.o. Died from pneumonia (autopsy)

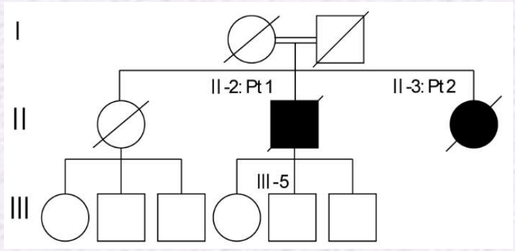
Saito *et al. Acta Neuropathologica Communications* (2020) 8:134
https://doi.org/10.1186/s40478-020-01008-2

Acta Neuropathologica Communications

LETTER TO THE EDITOR Open Access

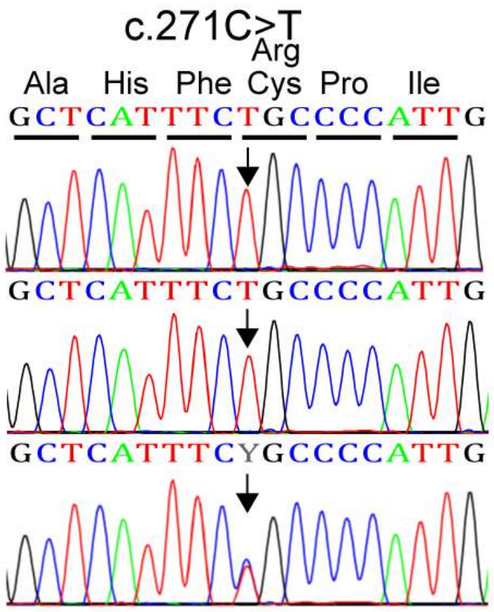
Novel *CHP1* mutation in autosomal-recessive cerebellar ataxia: autopsy features of two siblings

Rie Saito[1*†], Norikazu Hara[2], Mari Tada[1*†], Yoshiaki Honma[3], Akinori Miyashita[2], Osamu Onodera[4], Takeshi Ikeuchi[2] and Akiyoshi Kakita[1]

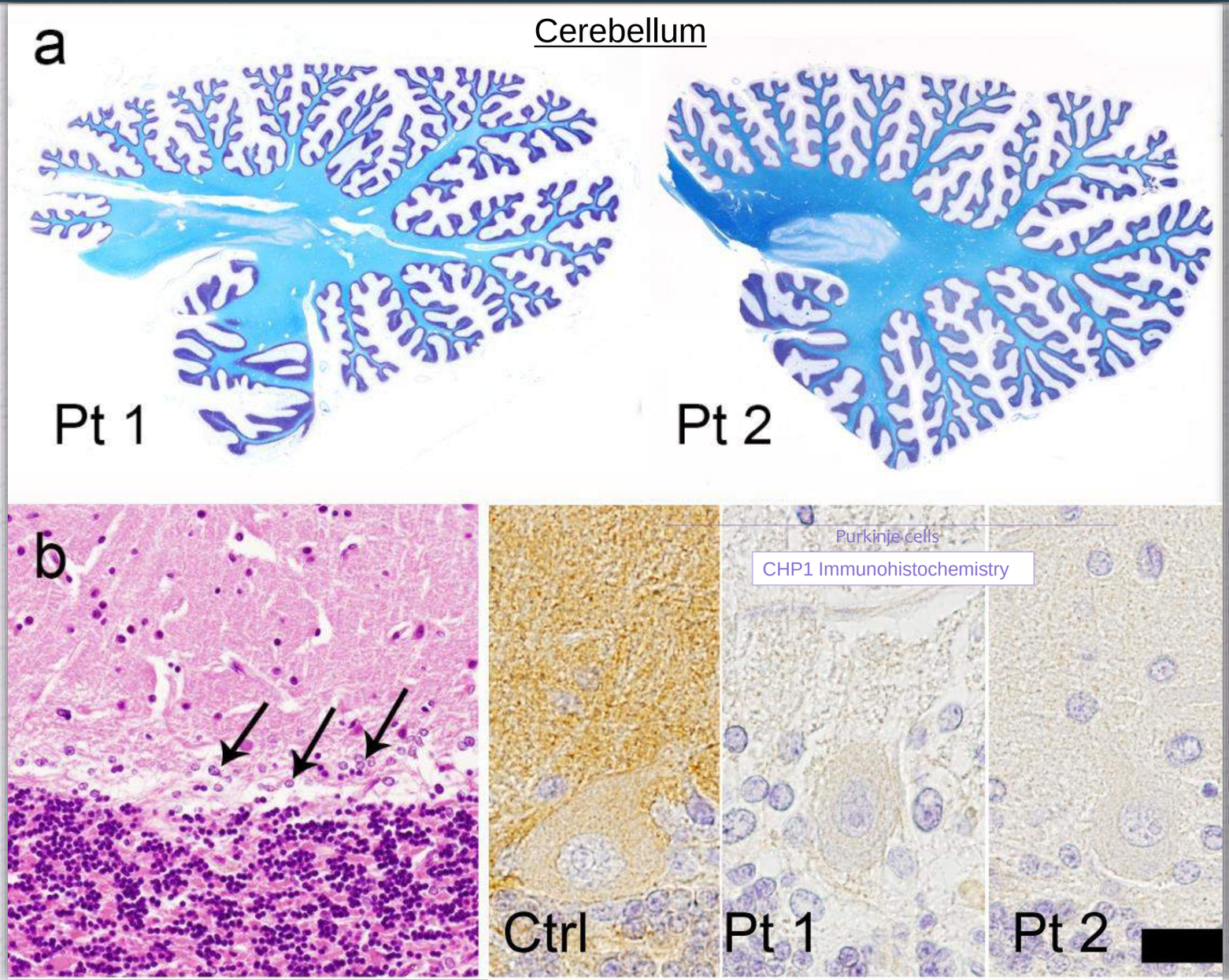


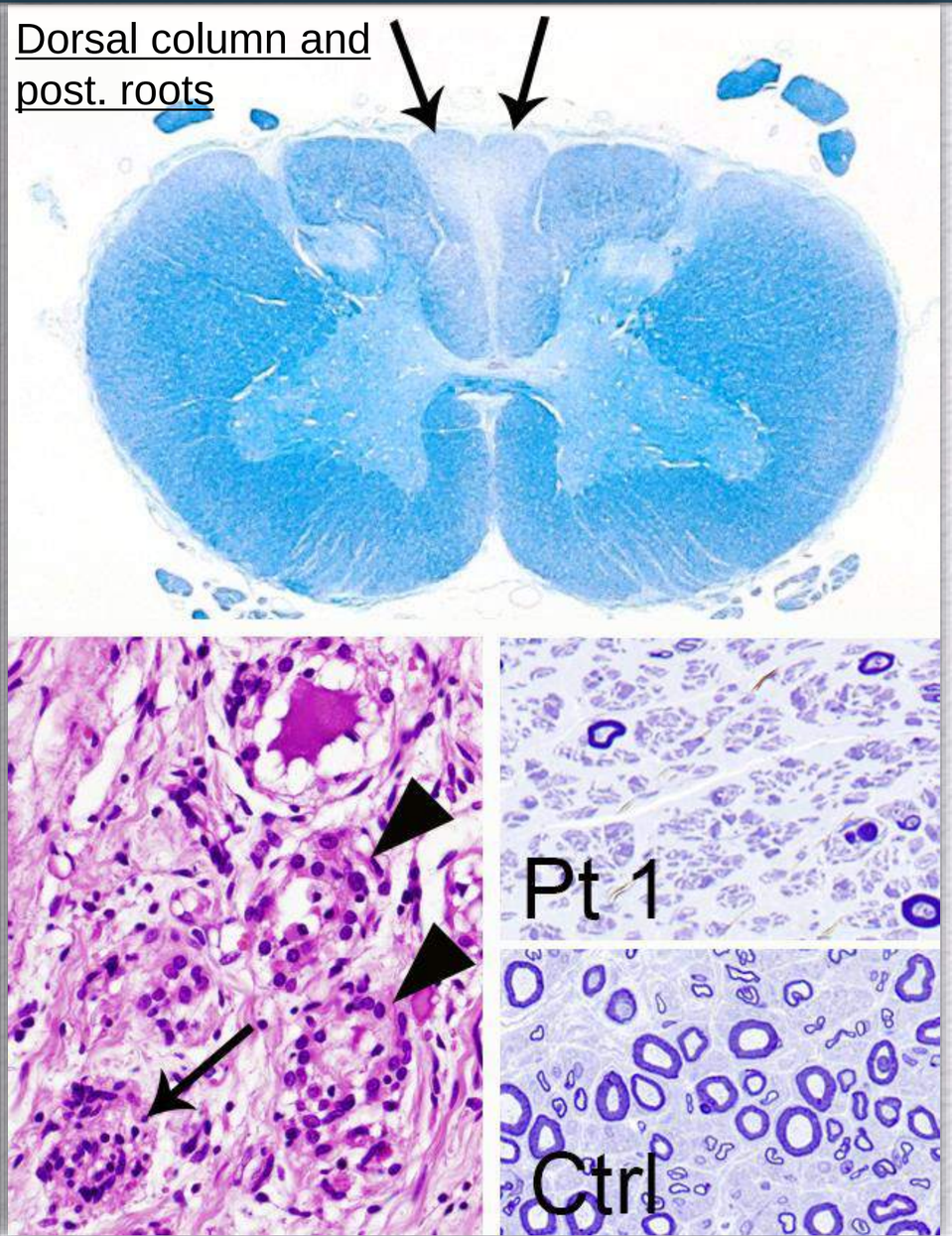
Whole-exome sequencing

novel *CHP1* mutation



ARCA-*CHP1*


a
Cerebellum
Pt 1
Pt 2
b
Purkinje cells
CHP1 Immunohistochemistry
Ctrl
Pt 1
Pt 2


Dorsal column and post. roots
Pt 1
Ctrl

ARCA: *SYNE1-ataxia*

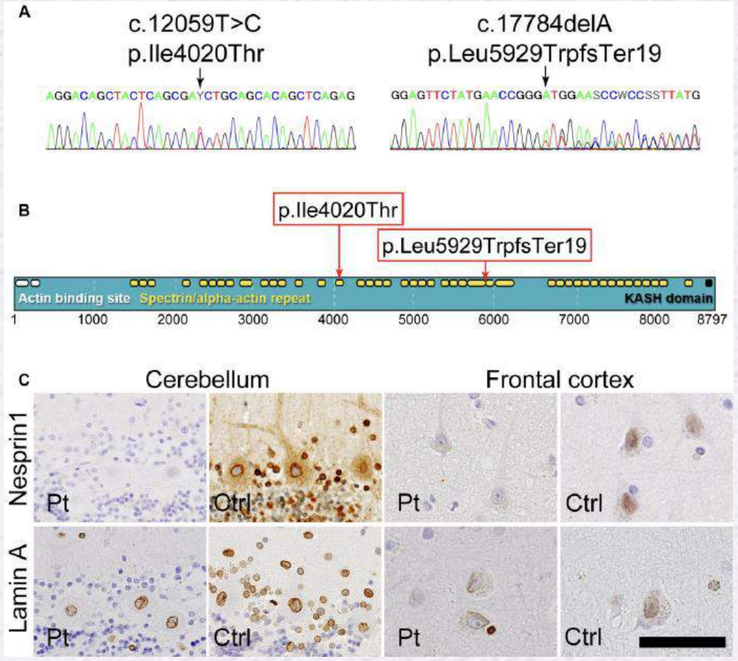
Journal of Neuropathology & Experimental Neurology, 2023, **82**, 267–271
https://doi.org/10.1093/jnen/nlac120
Advance access publication 16 December 2022
Letter to the Editor

OXFORD

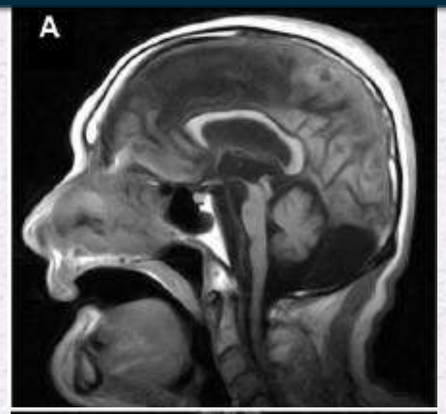
Letter to the Editor

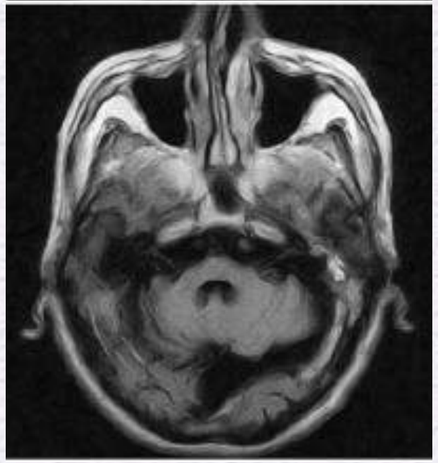
SYNE1-ataxia: clinicopathologic features of an autopsied patient with novel compound heterozygous mutations

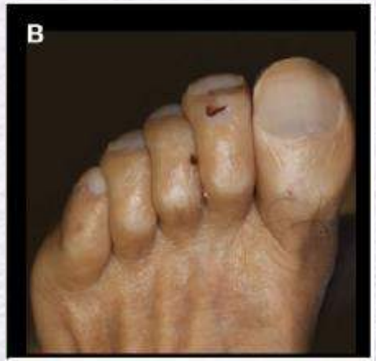
Rie Saito, MD, PhD,[1] Norikazu Hara, PhD,[2] Mari Tada, MD, PhD,[1]*
Masatoshi Wakabayashi, MD, PhD,[3] Akinori Miyashita, PhD,[2]
Masatoyo Nishizawa, MD, PhD,[4] Osamu Onodera, MD, PhD,[4]
Takeshi Ikeuchi, MD, PhD,[2] Akiyoshi Kakita, MD, PhD[1]

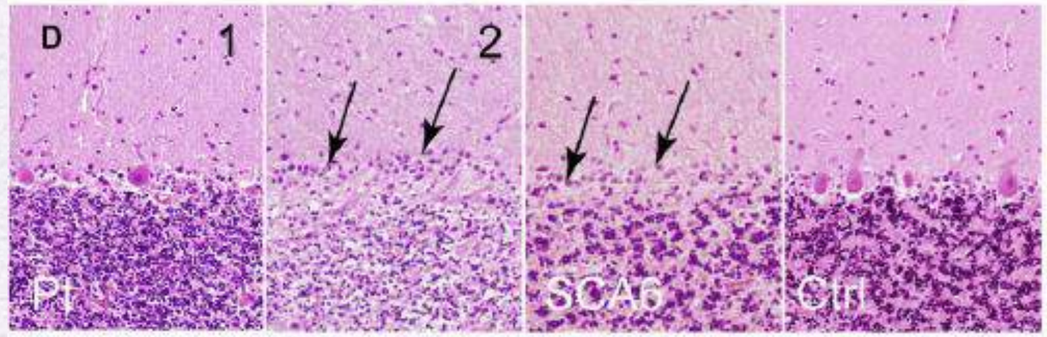


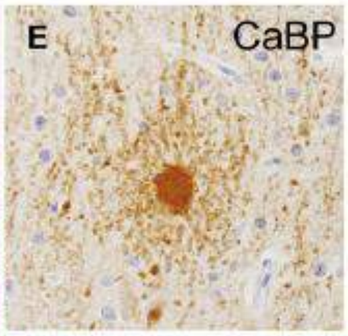
Journal of Neuropathology & Experimental Neurology, 2023, 82, 267–271

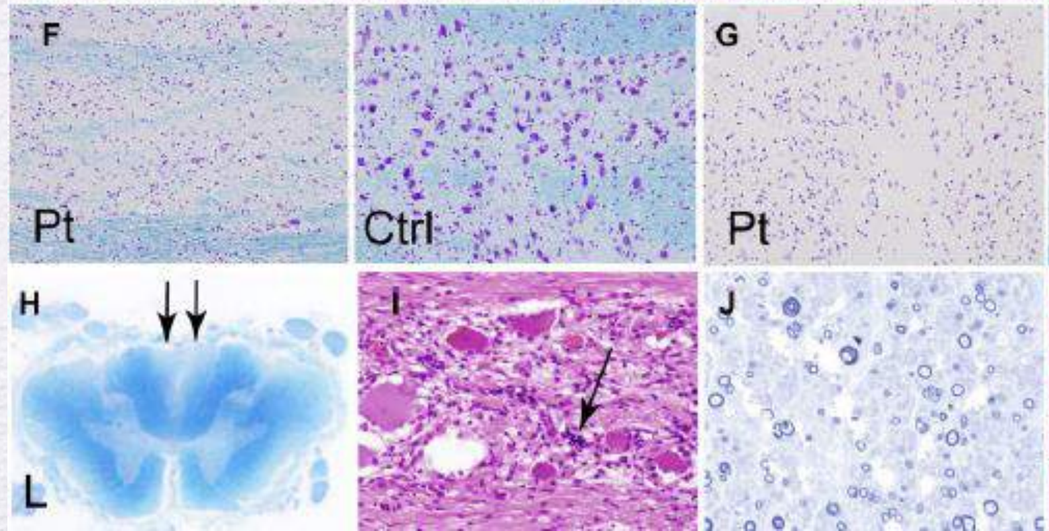












SCA17-digenic *TBP/STYB1* disease

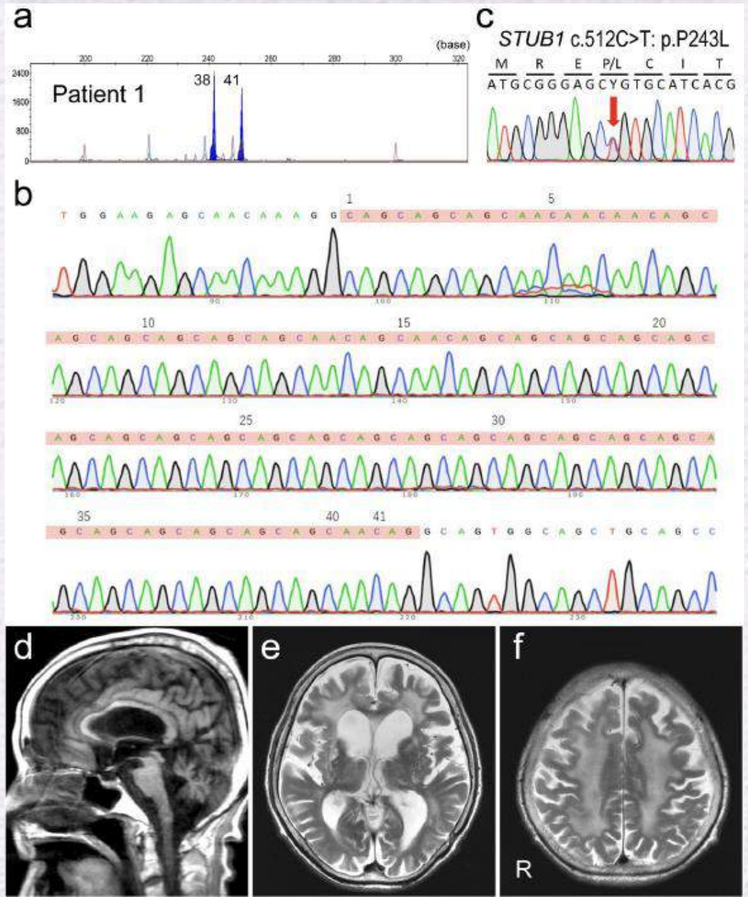
Saito et al.
Acta Neuropathologica Communications (2022) 10:177
https://doi.org/10.1186/s40478-022-01486-6

Acta Neuropathologica Communications

CASE REPORT Open Access

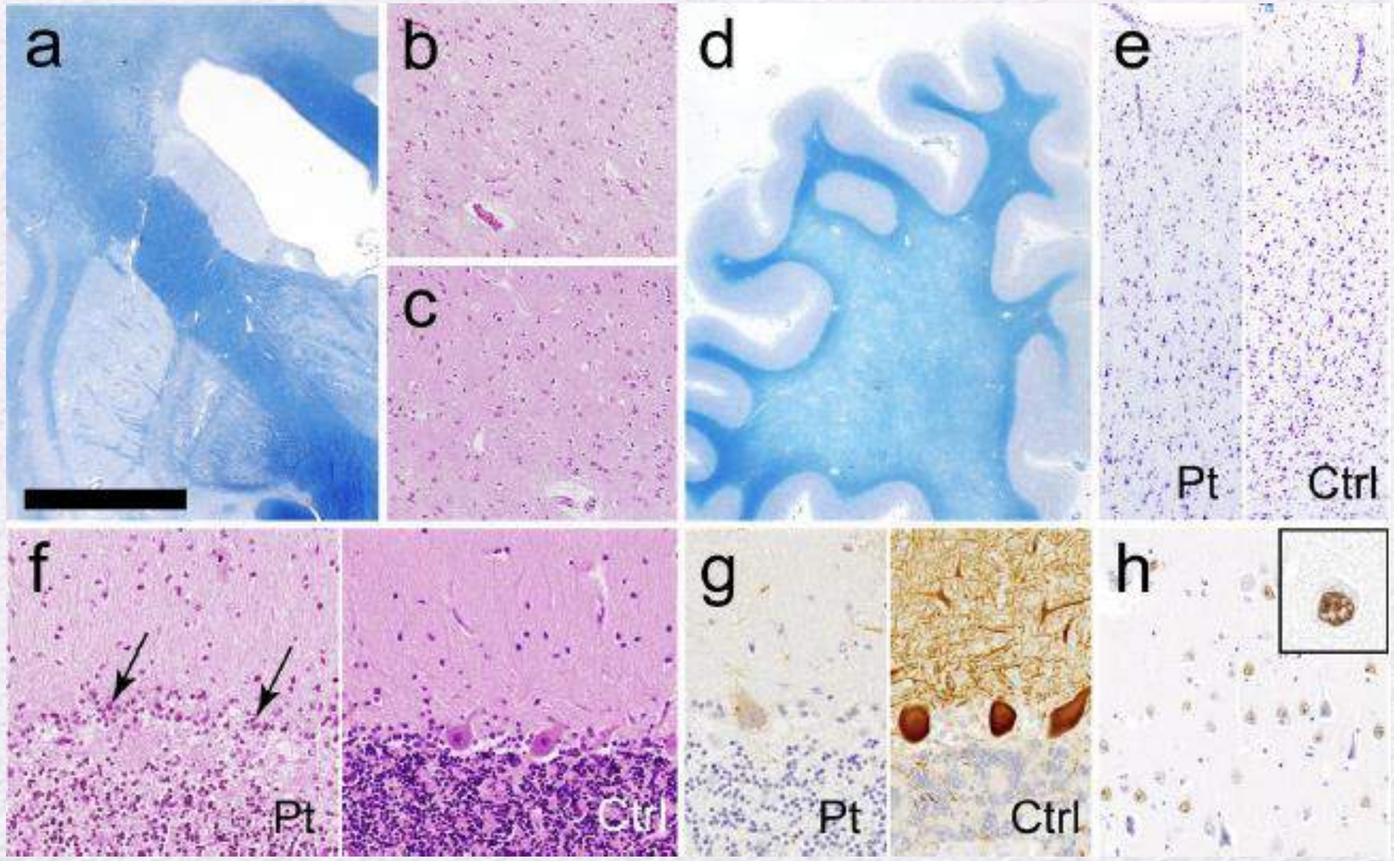
Spinocerebellar ataxia type 17-digenic *TBP/STUB1* disease: neuropathologic features of an autopsied patient

Rie Saito[1], Yui Tada[2], Daisuke Oikawa[3], Yusuke Sato[4], Makiko Seto[5], Akira Satoh[5], Kodai Kume[2], Nozomi Ueki[6], Masahiro Nakashima[6], Shintaro Hayashi[1,7], Yasuko Toyoshima[1,8], Fuminori Tokunaga[3], Hideshi Kawakami[2] and Akiyoshi Kakita[1,9*]



Caused by digenic inheritance of two gene mutations
- (1) intermediate polyglutamine-encoding CAG/CAA repeat expansions (polyQ) in *TBP* (*TBP*41-49)
  - → associated with SCA17
- (2) *STUB1* heterozygosity
  - → associated with SCA48 and SCA16 (autosomal recessive)

We experienced identical twin siblings, one of whom was autopsied and was found to carry an intermediate allele (41 and 38 CAG/CAA repeats) in *TBP* and a heterozygous missense mutation in *STUB1* (p.P243L). These patients developed autosomal recessive Huntington's disease-like symptoms.



Neuropathology and Neuroimaging Integrated Education Course for Movement Disorders
February 16-17, 2024 • Seoul, Korea
International Parkinson and Movement Disorder Society Asian & Oceanian Section

Neuropathology of MSA and SCAs

MSA

Autosoma Dominant disorders
SCA6, DRPLA, SCA3/MJD, SCA2, SCA31

Autosomal Recessive disorders
ARCA-*CHP1*, *SYNE1*-ataxia, SCA17-DI

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