64th Annual Diagnostic Slide Session 2023
Case #3

DATE: JUNE 10, 2023 CASE SUBMITTED BY: ANFISA BAIANDUROVA, MD AND RANDY WOLTJER, MD, PhD

Clinical history

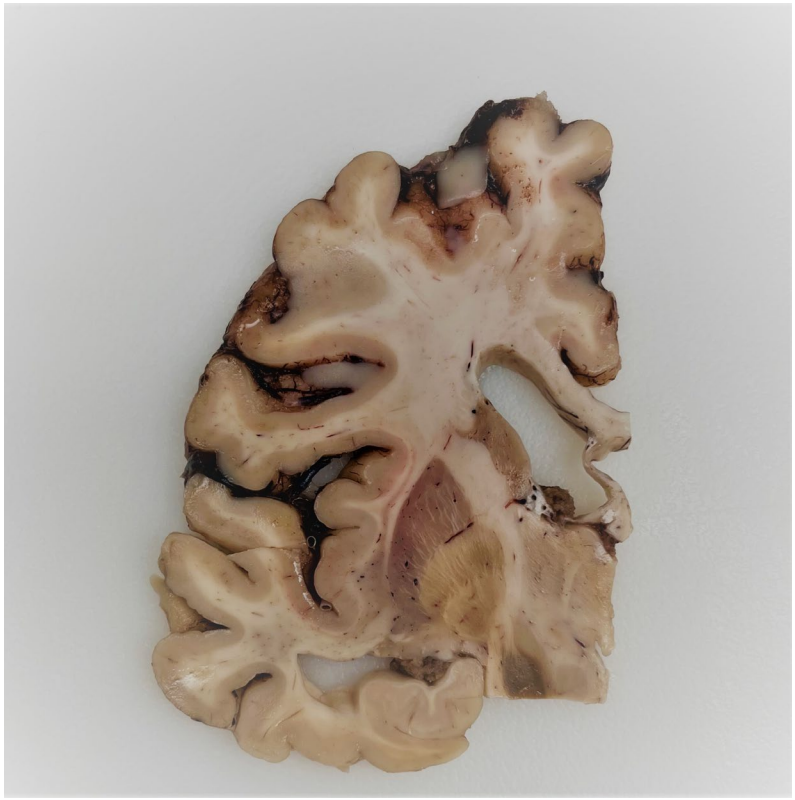
18-year-old male with cognitive developmental delay and ataxia since early childhood, that had been slowly progressing until early adolescence, when he had a rapid progression of dementia and parkinsonism.

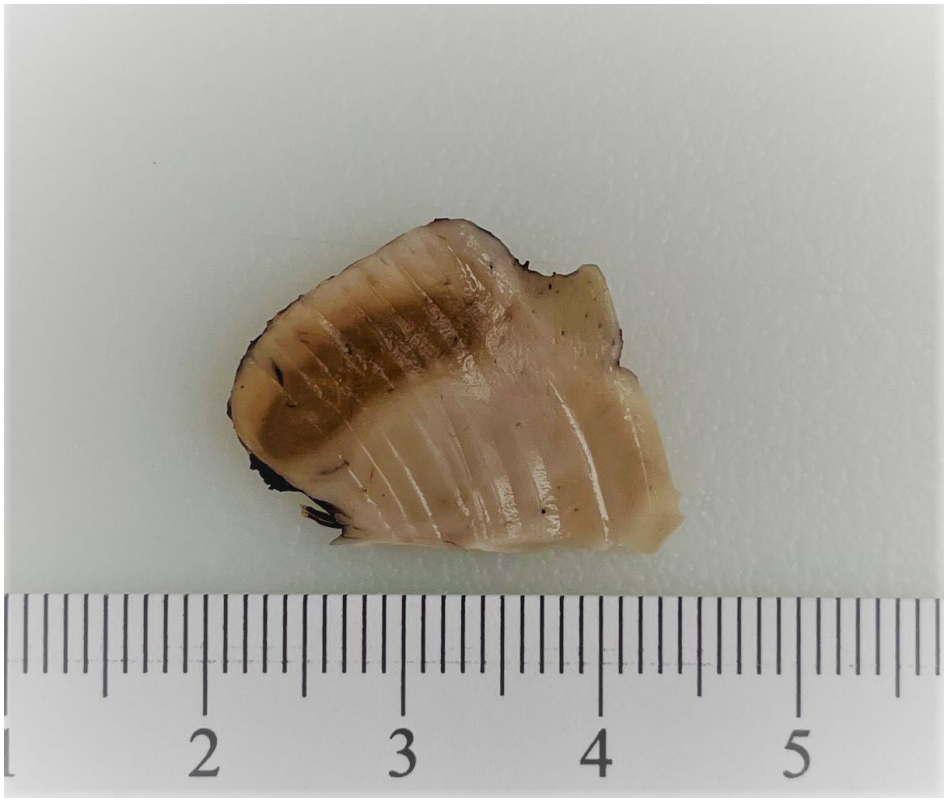
MRI findings:

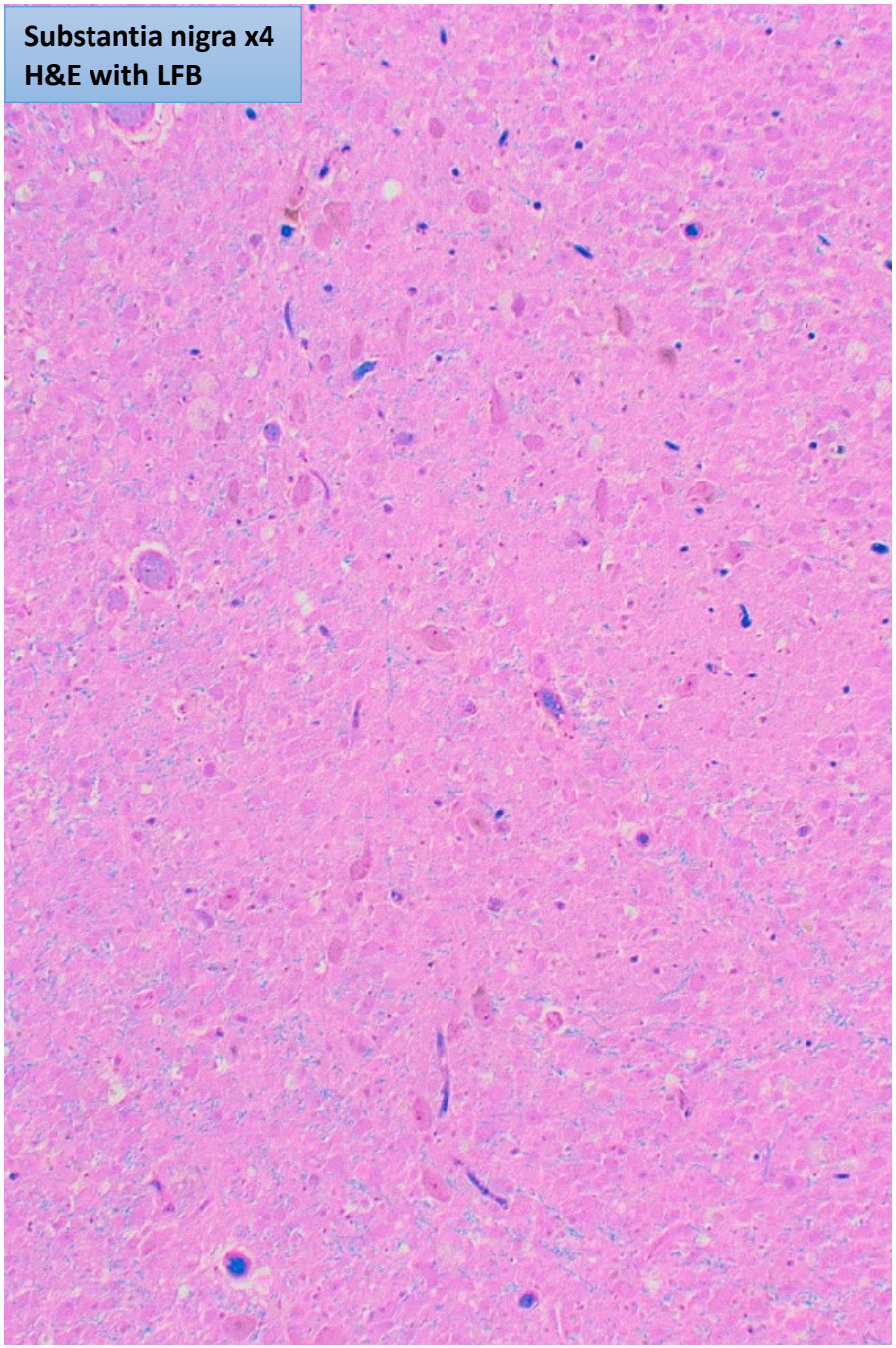
- T2 hypointensity in globus pallidus.
- T1 hyperintense halo surrounding a central linear band of hypointensity in the substantia nigra and cerebral peduncles.

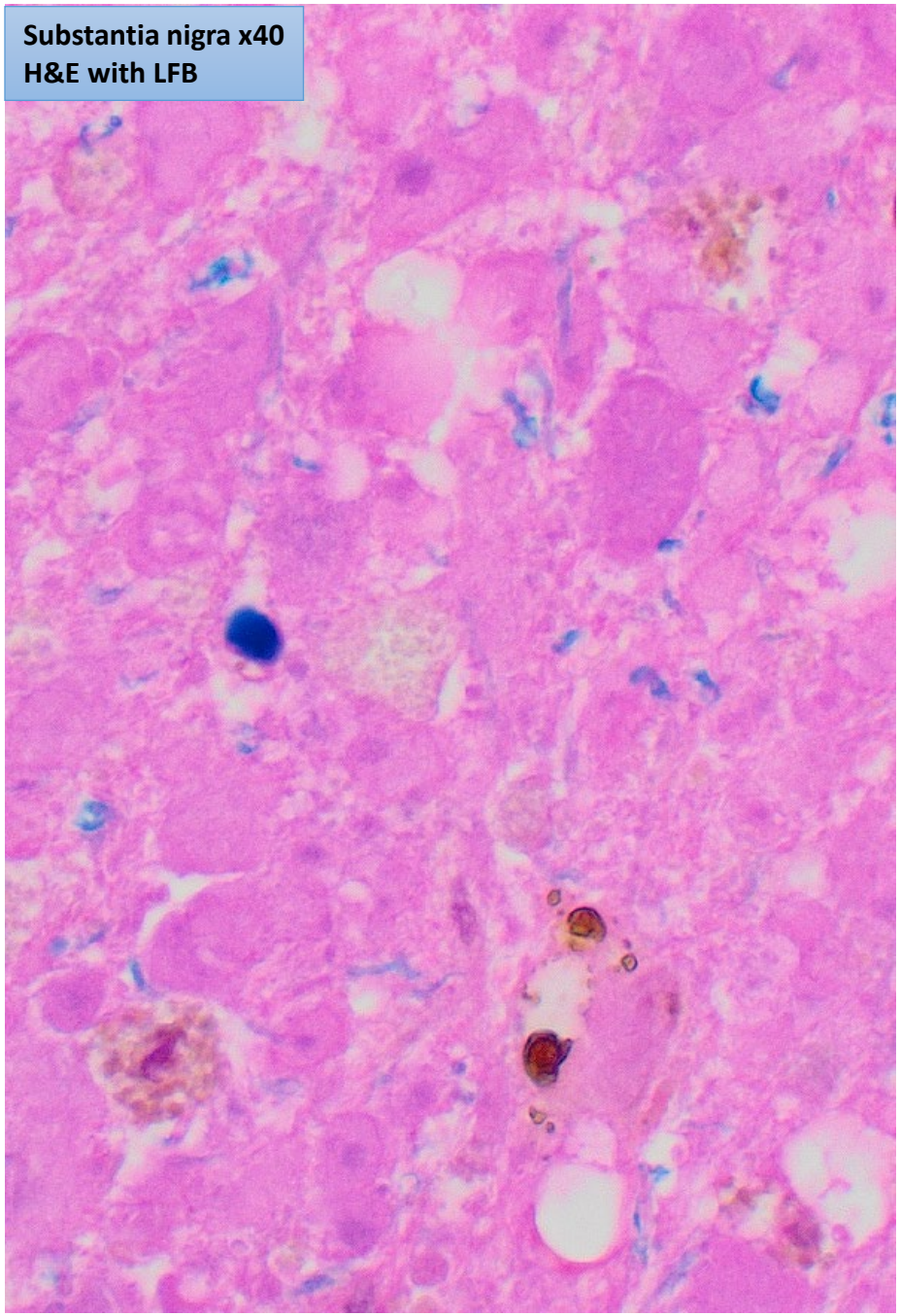
Gross findings

Brain weight (fixed): 887 g
Mild cortical atrophy involving the frontal, parietal, and temporal lobes.
Dark-brown discoloration of globus pallidus and substantia nigra, more prominent in the latter.






Substantia nigra x4
H&E with LFB

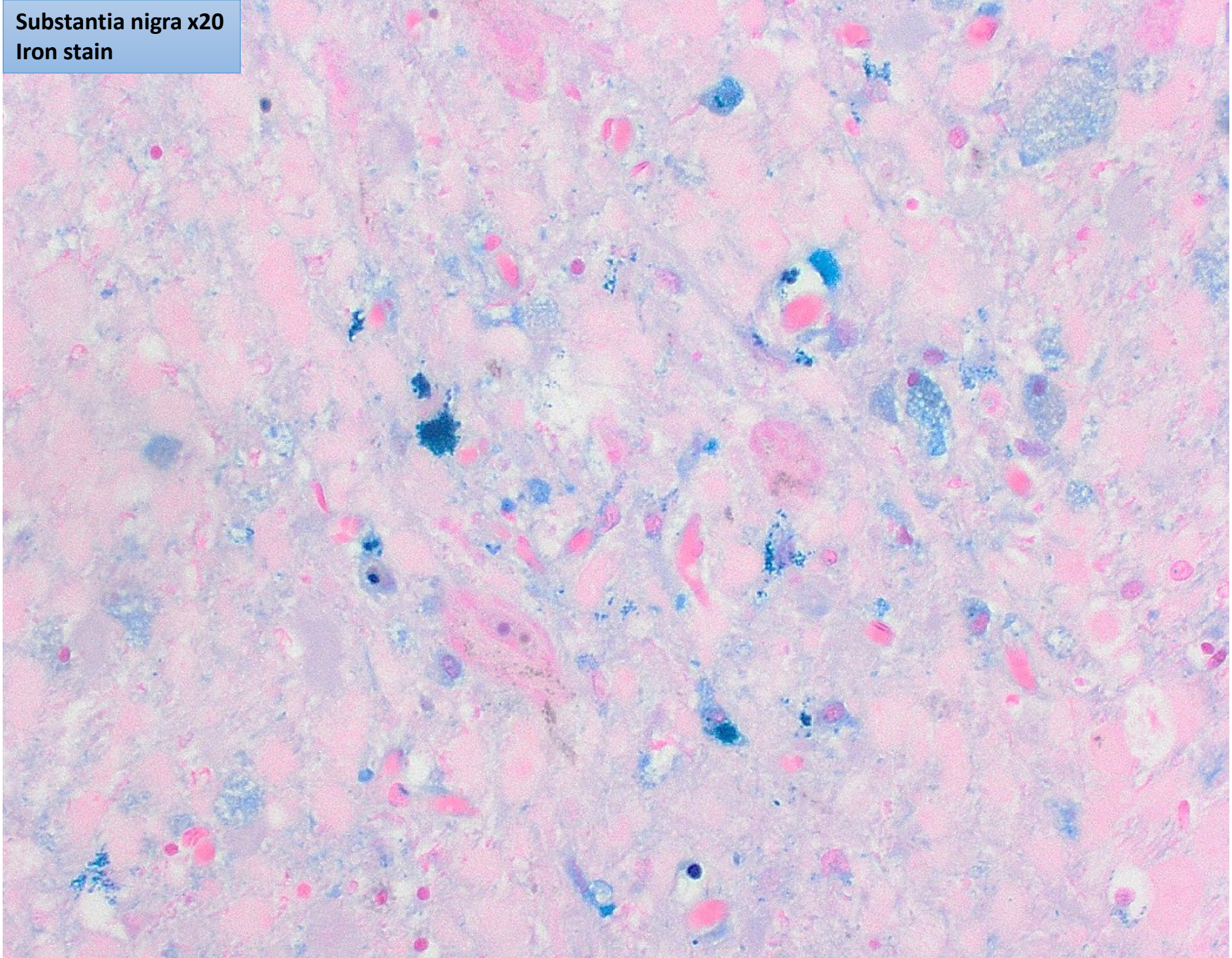

Substantia nigra x40
H&E with LFB

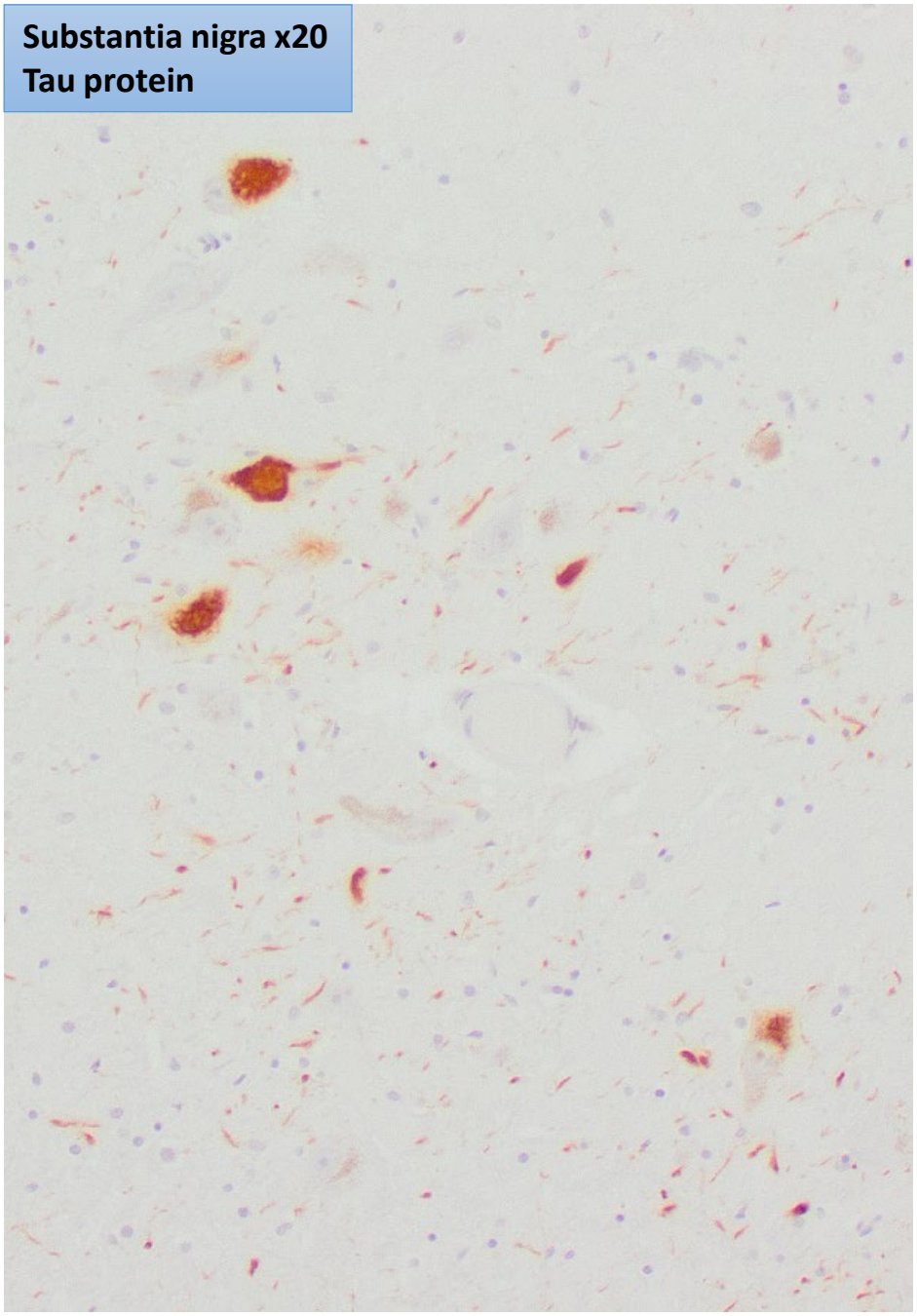
Discussion

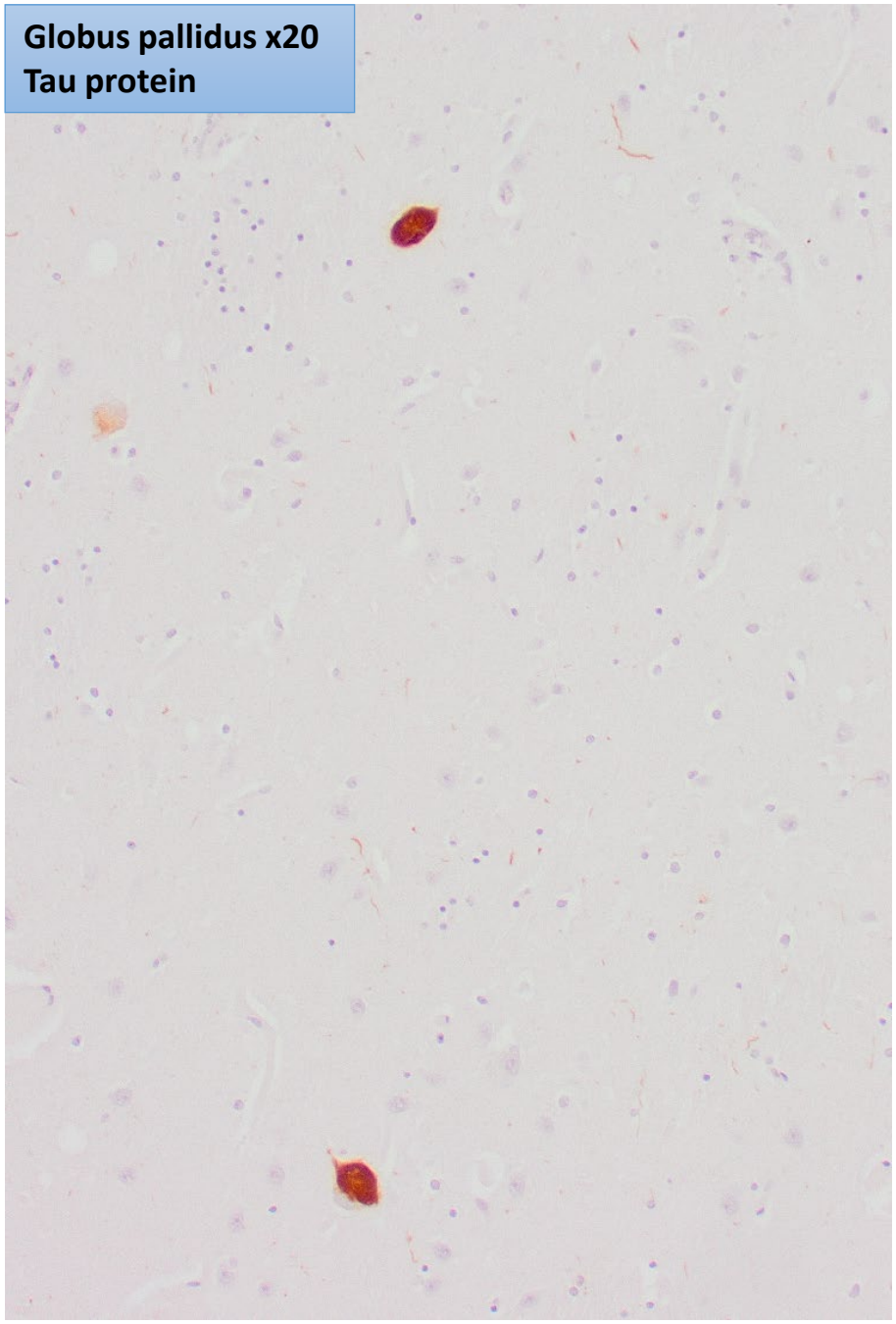
- Differential diagnosis
- Further workup

Differential diagnosis:

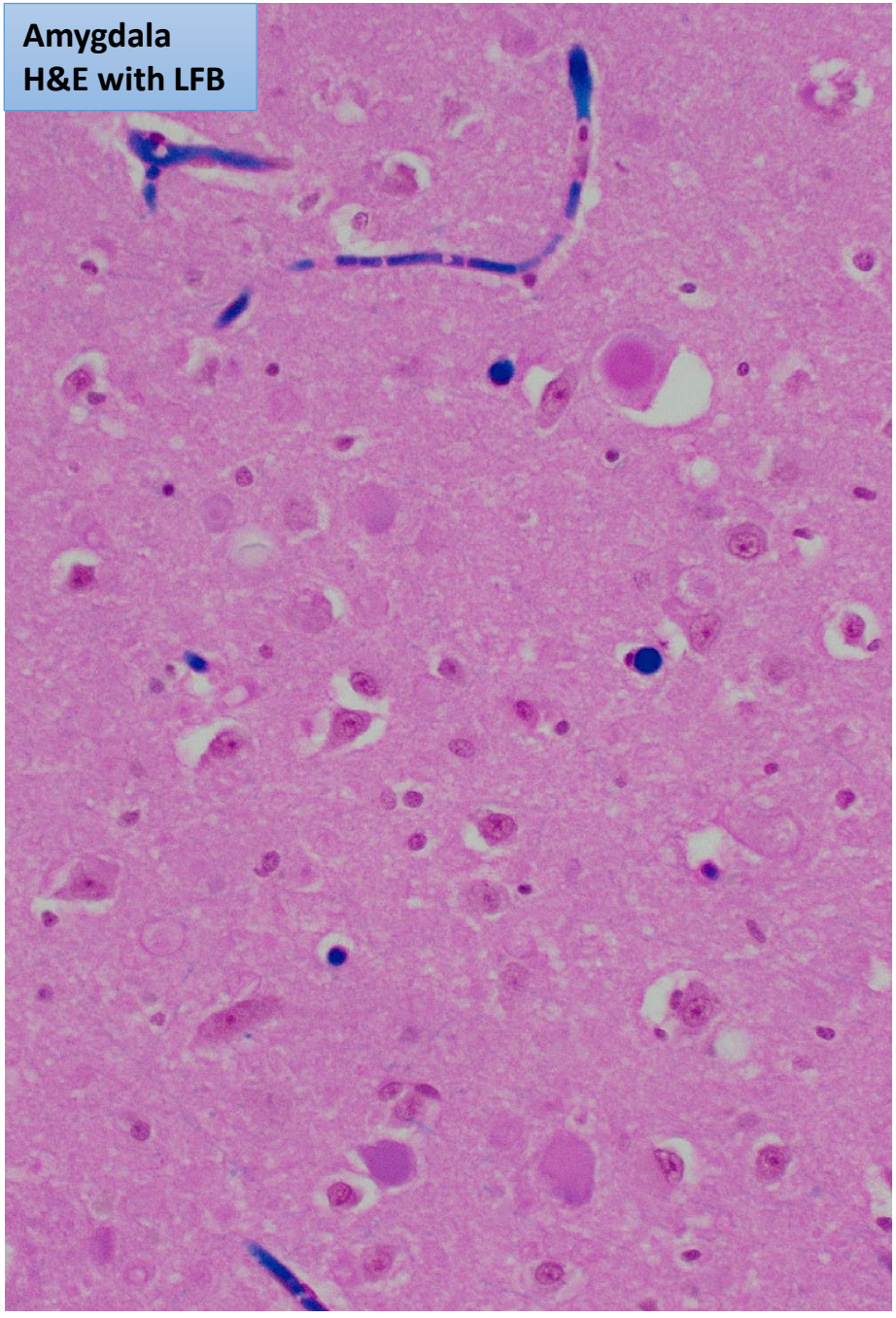
- Neurodegeneration with brain iron accumulation
- Wilson’s disease ?
- Hemochromatosis ?


Substantia nigra x20
Iron stain

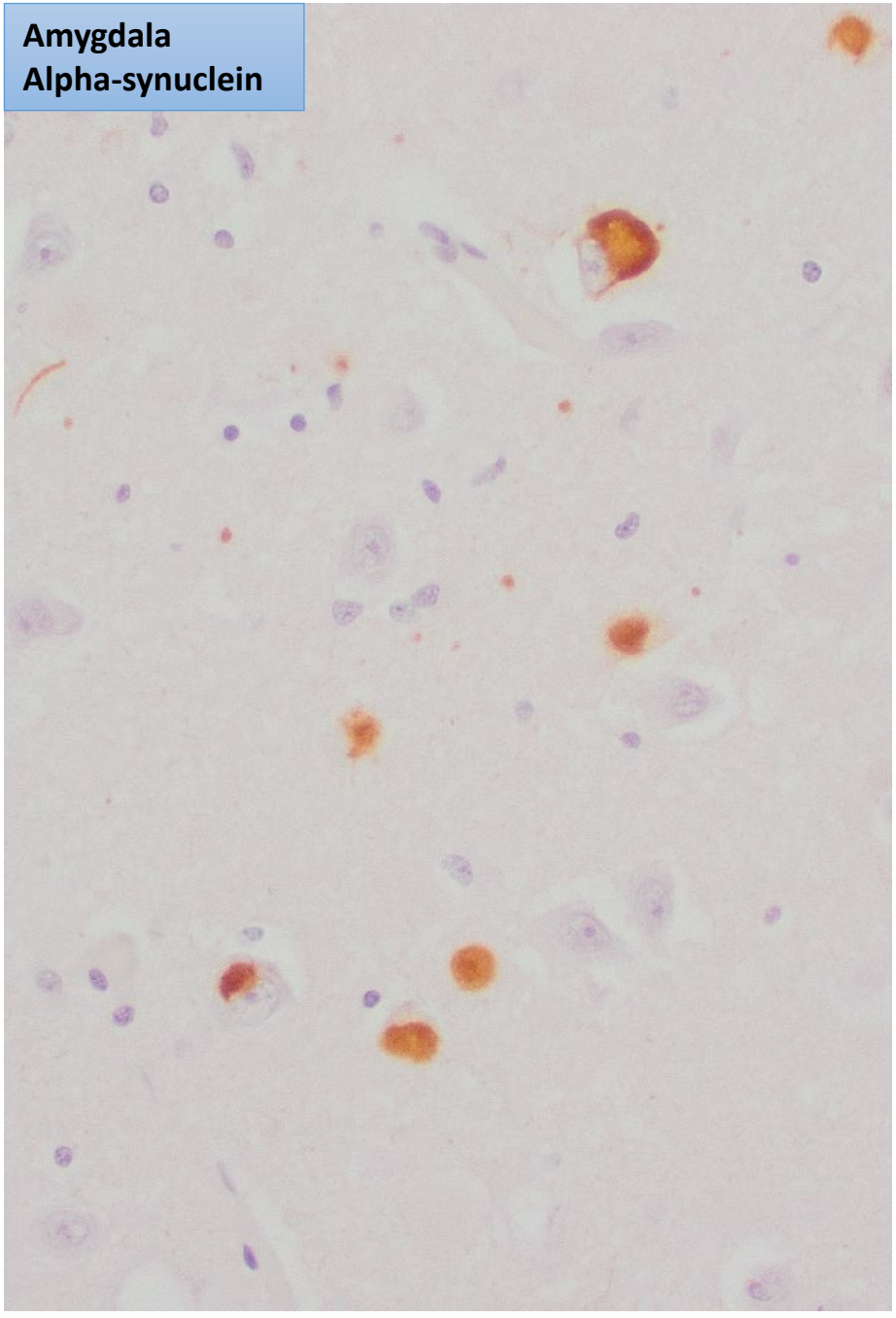

Substantia nigra x20
Tau protein


Globus pallidus x20
Tau protein

Amygdala
H&E with LFB



Amygdala
Alpha-synuclein



Additional microscopy findings

- Tau immunohistochemistry revealed neurofibrillary tangles and dystrophic neurites in the cerebrum and basal ganglia

- Alpha-synuclein immunohistochemistry revealed relatively rare Lewy bodies and neurites in the cerebrum and basal ganglia

- No beta-amyloid deposits identified

- No lesions of TDP-43

Antemortem genetic testing revealed a pathogenic mutation in the WDR45 gene located on the X chromosome.

FINAL NEUROPATHOLOGIC DIAGNOSIS:
Beta-propeller protein-associated neurodegeneration (BPAN)

Beta-propeller protein-associated neurodegeneration (BPAN) is one of the several neurodegenerative disorders with brain iron accumulation (NBIA).

NBIAs have similar pathologic changes that are observed in selectively vulnerable brain regions, which suggests similar pathophysiology.

The main clinical features of NBIA include: progressive dystonia, dysarthria, spasticity, parkinsonism, optic atrophy

Disorder	Estimated prevalence per million	Inheritance	Clinical features
BPAN	2–3	X-linked dominant	Global developmental delay, epilepsy, dystonia, parkinsonism in adulthood
PKAN	2	Autosomal recessive	Classic: severe, progressive dystonia, retinal degeneration Atypical: speech disorders, dystonia, psychiatric symptoms
PLAN	1	Autosomal recessive	INAD: psychomotor regression, ataxia, dystonia, spasticity, optic atrophy aNAD: speech delay, developmental regression, dystonia, spasticity, optic atrophy PLA2G6-related dystonia-parkinsonism: parkinsonism, dystonia, cognitive decline, psychiatric changes
MPAN	1	Autosomal recessive	Impaired gait, spasticity, weakness, dystonia, psychiatric changes, optic atrophy, parkinsonism
FAHN	<1	Autosomal recessive	Spasticity, dysarthria, optic atrophy, intellectual impairment
CoPAN	<1	Autosomal recessive	Spasticity, oromandibular dystonia, dysarthria, neuropathy, parkinsonism

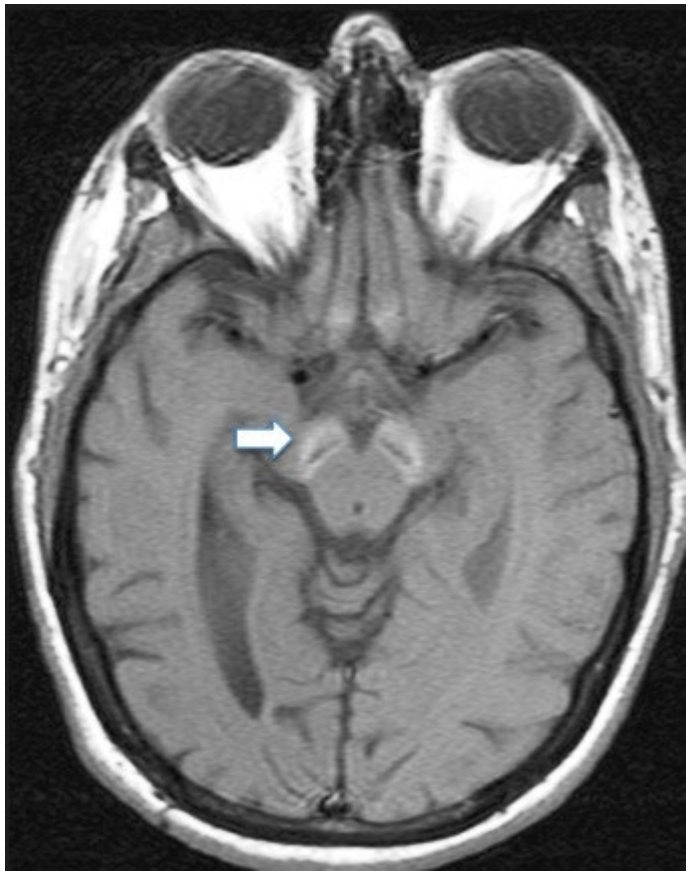
NBIA, neurodegeneration with brain iron accumulation; BPAN, beta-propeller protein-associated neurodegeneration; PKAN, pantothenate kinase-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; INAD, infantile neuroaxonal dystrophy; aNAD, atypical neuraxonal dystrophy; MPAN, mitochondrial membrane protein-associated neurodegeneration; FAHN, fatty acid hydroxylase-associated neurodegeneration; CoPAN, COASY protein-associated neurodegeneration.

Wilson JL, Gregory A, Kurian MA, Bushlin I, Mochel F, Emrick L, Adang L; BPAN Guideline Contributing Author Group; Hogarth P, Hayflick SJ. Consensus clinical management guideline for beta-propeller protein-associated neurodegeneration. Dev Med Child Neurol. 2021 Dec;63(12):1402-1409.

Diagnostic evaluation

A diagnosis of NBIA is often suspected based on brain MRI evidence for increased basal ganglia iron along with characteristic clinical features.

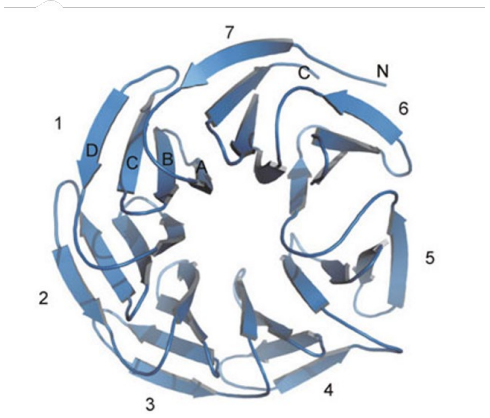
Disorder	Major clinical features	MRI features
PKAN	Dystonia, parkinsonism, spasticity, pigmentary retinopathy, acanthocytosis, neuropsychiatric features	T2 hyperintense signal surrounded by hypointense signal in globus pallidus, less involvement of substantia nigra, representing the "eye of the tiger" sign
PLAN	Psychomotor regression, ataxia, autism, dystonia, parkinsonism, optic atrophy	Iron seen later in disease, affecting globus pallidus and substantia nigra equally, cerebellar atrophy and gliosis, less often cerebral atrophy
MPAN	Spasticity, dystonia, dementia, peripheral nerve involvement	Iron affecting globus pallidus and substantia nigra equally, prominent medial medullary lamina streak on T2 sequences
BPAN	Intellectual disability, little to no language, mixed seizure types, juvenile parkinsonism, autism	T2 hypointense signal in substantia nigra even greater than globus pallidus, T1 bright "halo" in substantia nigra/cerebellar peduncles, changes may be seen in early childhood



T_1 imaging demonstrates the hyperintense **halo** surrounding a central linear band of hypointensity in the substantia nigra and cerebral peduncles in a patient with BPAN.

Hayflick SJ, Kurian MA, Hogarth P. Neurodegeneration with brain iron accumulation. Handb Clin Neurol. 2018;147:293-305.

BPAN is an X-linked dominant disorder caused by mutations in WDR45 gene.



The human *WDR45* gene encodes a WDR45 protein which has a β-propeller structure.

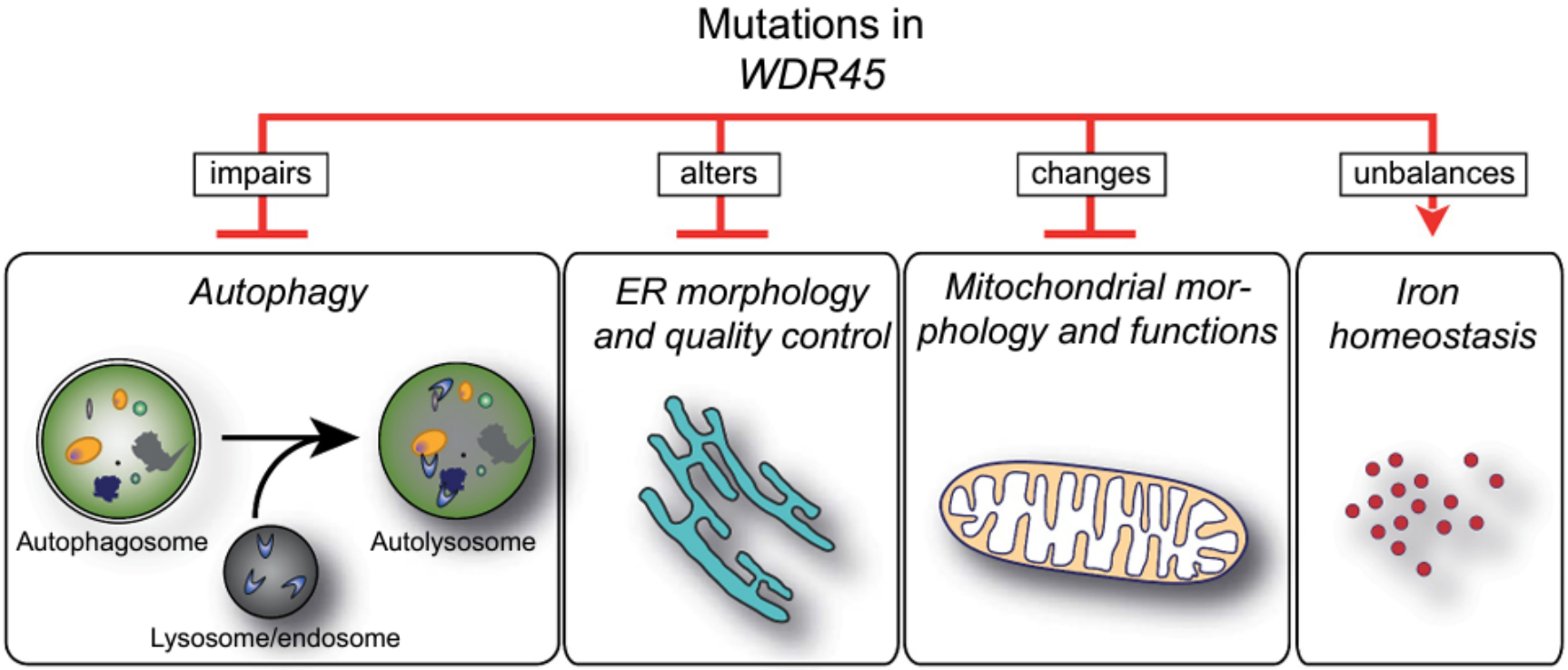
WDR45 belongs to a large family of WD40 repeat protein and is believed to be an important regulator of autophagy.

So far, 93 patients carrying a WDR45 variant have been conclusively associated to BPAN. 84 of them are females while only 9 are male.

Xu C, Min J. Structure and function of WD40 domain proteins. Protein Cell. 2011 Mar;2(3):202-14. doi: 10.1007/s13238-011-1018-1. Epub 2011 Apr 6.

WDR45 function

The precise cellular function of WDR45 is still largely unknown, but deletions or conventional variants in *WDR45* can lead to autophagy defects, malfunctioning mitochondria, endoplasmic reticulum stress and unbalanced iron homeostasis.



Xu C, Min J. Structure and function of WD40 domain proteins. Protein Cell. 2011 Mar;2(3):202-14. doi: 10.1007/s13238-011-1018-1. Epub 2011 Apr 6.

Take Home Messages

BPAN is a hereditary neurodegenerative disease due to mutation in WDR45, affecting younger patients.

It has a distinct clinical and radiologic features.

Pathology is remarkable for iron accumulation, tau and alpha-synuclein positive neuronal inclusions. There is also a large component of axonal dystrophy, not seen in many other diseases.

There is link between WDR45 with BPAN, but the exact pathogenesis is still not clear.

References

1. Hayflick SJ, Kurian MA, Hogarth P. Neurodegeneration with brain iron accumulation. Handb Clin Neurol. 2018;147:293-305.

2. Wilson JL, Gregory A, Kurian MA, Bushlin I, Mochel F, Emrick L, Adang L; BPAN Guideline Contributing Author Group; Hogarth P, Hayflick SJ. Consensus clinical management guideline for beta-propeller protein-associated neurodegeneration. Dev Med Child Neurol. 2021 Dec;63(12):1402-1409

3. Gregory A, Kurian MA, Haack T, Hayflick SJ, Hogarth P. Beta-Propeller Protein-Associated Neurodegeneration. 2017 Feb 16. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023.

4. Paudel R, Li A, Wiethoff S, Bandopadhyay R, Bhatia K, de Silva R, Houlden H, Holton JL. Neuropathology of Beta-propeller protein associated neurodegeneration (BPAN): a new tauopathy. Acta Neuropathol Commun. 2015 Jun 30;3:39.

5. Cong Y, So V, Tijssen MAJ, Verbeek DS, Reggiori F, Mauthe M. *WDR45*, one gene associated with multiple neurodevelopmental disorders. Autophagy. 2021 Dec;17(12):3908-3923.

6. Xu C, Min J. Structure and function of WD40 domain proteins. Protein Cell. 2011 Mar;2(3):202-14. doi: 10.1007/s13238-011-1018-1. Epub 2011 Apr 6.