Multiomic profiling reveals aberrant immunomodulatory signature in β-propeller protein-associated neurodegeneration patient iPSC-derived microglia

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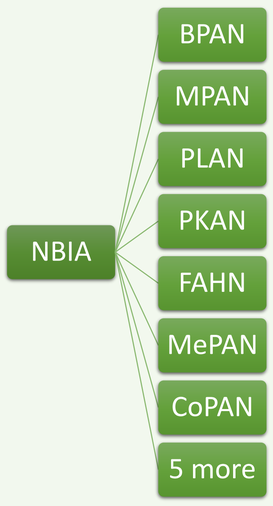
Introduction

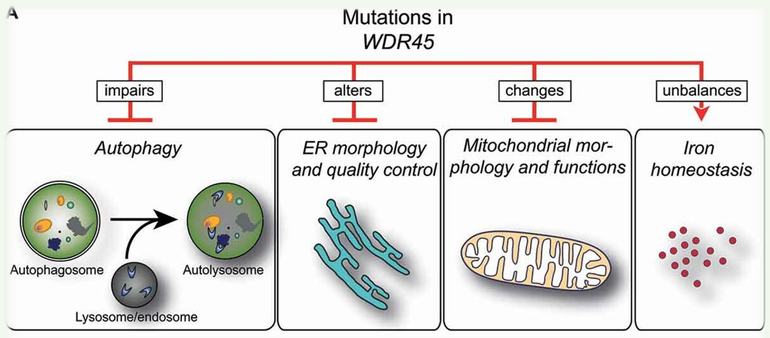


- ß-propeller protein associated neurodegeneration (BPAN) is a part of Neurodegeneration with Brain Iron Accumulation (NBIA) disorder.
- NBIA is characterized by iron accumulation generally observed in the globus pallidus and substantia nigra
- BPAN follows a biphasic clinical course

Beginning in early childhood
- global developmental delay
- intellectual disability
- epilepsy
- fine and gross motor impairment
- abnormal behaviour reminiscent of autism spectrum disorder

The second phase begins in early adulthood
- progressive cognitive decline
- dementia
- movement disorders including parkinsonism and dystonia.

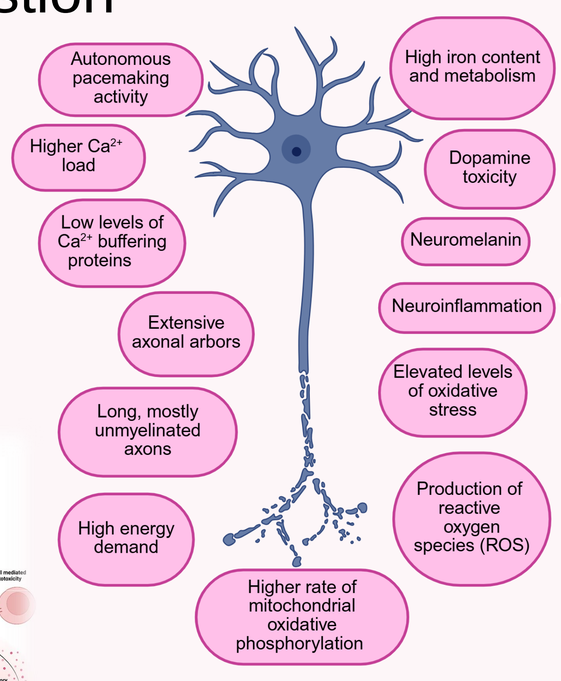
- BPAN is a rare monogenic neurodegenerative disorder caused by de novo mutations in the WDR45 gene, which encodes a WD-repeat protein essential for autophagy regulation.

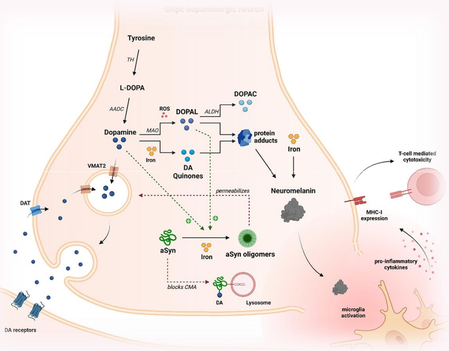


Cong Y, 2021

Research Question

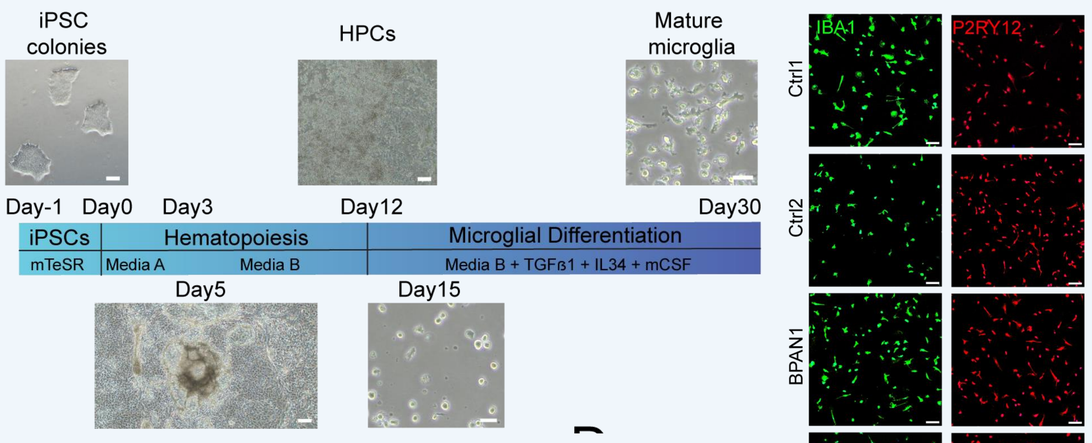
What is the cause of selective vulnerability of dopaminergic neurons (in BPAN patients)?





Wise, R. M., 2022

Method



iPSC lines from two patients carrying heterozygous WDR45 mutations, c.519+1_519+3delGTG (BPAN 1) and c.344+2T>G in exon 6 (BPAN 2)
Protocol by McQuade et al., 2018 with modifications

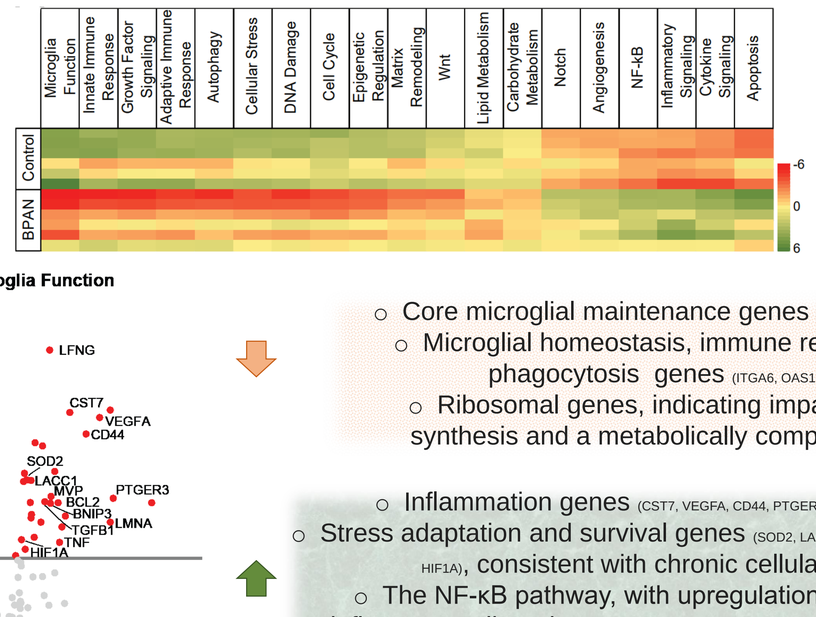
References

Cong Y. et al., *WDR45*, one gene associated with multiple neurodevelopmental disorders. Autophagy. 2021. doi: 10.1080/15548627.2021.1899669.

Wise, R. M. et al., (2022). Interactions of dopamine, iron, and alpha-synuclein linked to dopaminergic neuron vulnerability in Parkinson's disease and Neurodegeneration with Brain Iron Accumulation disorders. *Neurobiology of Disease*

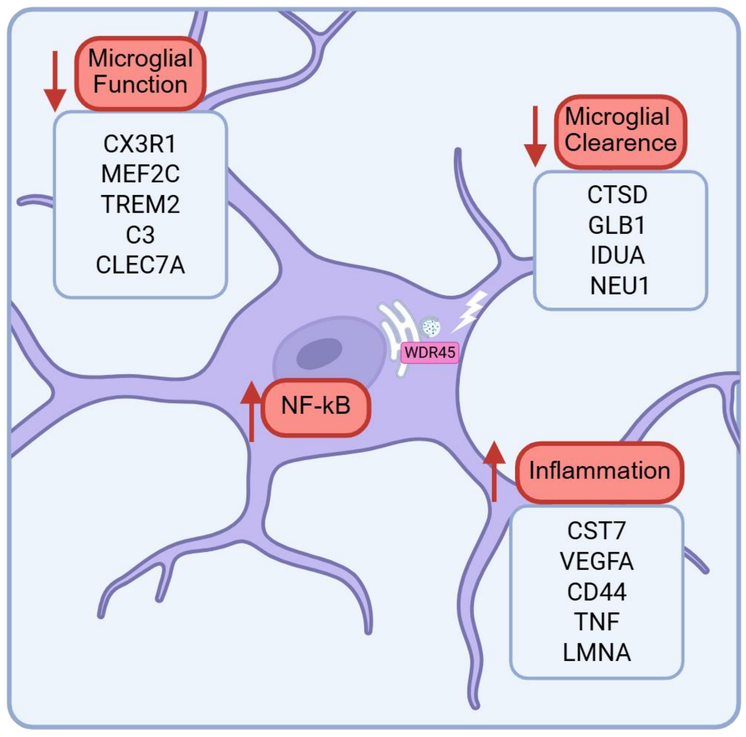
Results

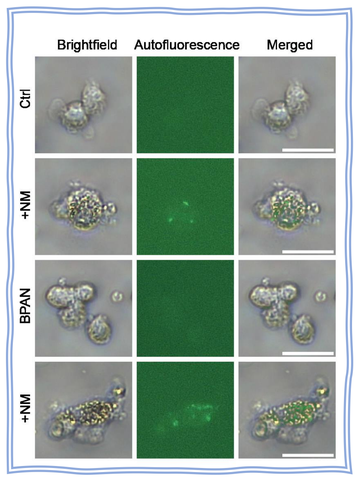
Targeted Transcriptomics



- Core microglial maintenance genes (CX3CR1, MEF2C, C3)
- Microglial homeostasis, immune resolution, and phagocytosis genes (ITGA6, OAS1, GBA, C3AR1)
- Ribosomal genes, indicating impaired protein synthesis and a metabolically compromised state.

- Inflammation genes (CST7, VEGFA, CD44, PTGER3, TNF, and LMNA)
- Stress adaptation and survival genes (SOD2, LACC1, MVP, TGFB1, BCL2, BNIP3, HIF1A), consistent with chronic cellular stress.
- The NF-κB pathway, with upregulation of key pro-inflammatory ligands (TNF, TNFSF12, LTB), receptors (LTBR, TNFRSF25), and intracellular mediators (TRAF2, TRAF3, MAP3K14, IKBKB).



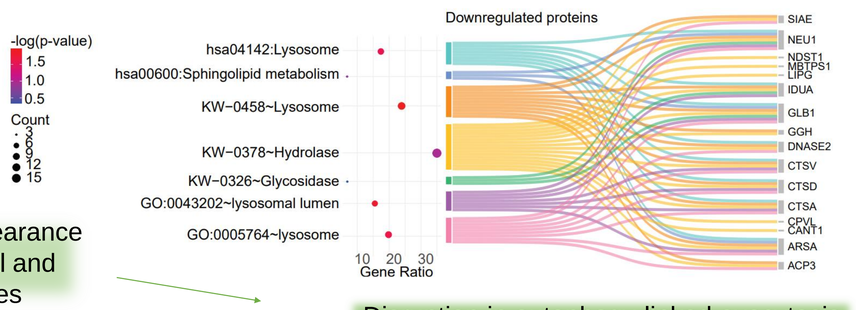


Secretomics

Reduced lysosomal enzymes (CTSD, GLB1, IDUA, and NEU1) and suppression of the complement component C3

Impaired microglial clearance of apoptotic material and protein aggregates

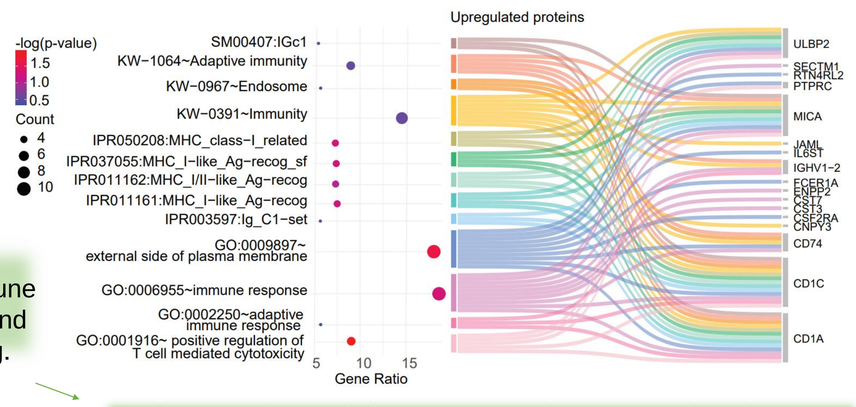
Disruption in autophagy-linked exocytosis



Increased secretion of immune mediators like antigen presentation molecules (CD74, MICA, CD1C, and ULBP2, cytokine receptor CSF2RA and protease MMP12

Reactive microglial state characterized by enhanced immune signaling, antigen processing, and extracellular matrix remodeling.

A shift toward a pro-inflammatory, antigen-presenting phenotype



Conclusion

- This is the first study to profile patient-derived microglia in BPAN, revealing a dysregulated, partial DAM-like phenotype.
- BPAN microglia show loss of homeostatic identity and upregulation of inflammatory and lysosomal pathways, consistent with a maladaptive immune state.
- These findings highlight microglia as likely contributors to BPAN neurodegeneration and as promising targets for therapeutic intervention.
- By uncovering microglial dysfunction in BPAN, this work broadens the focus beyond neurons and opens new avenues for understanding and treating this disorder.

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