WDR45 function and contribution to BPAN

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Mutations in the X-linked gene WDR45 cause Beta Propeller-protein associated Neurodegeneration (BPAN). WDR45 encodes for a protein typically associated with autophagy regulators, though the protein's function and how it's absence in BPAN patients leads to the disease state is largely unknown. To explore protein function, we used a bait-BioID system to label protein interactors with WDR45 in neuroblastoma cells. We found a strong association of WDR45 with proteins involved in endomembrane associate protein transport, RNA processing, and mitochondrial proteins important for metabolism of lipids and maintaining mitochondrial membrane potential. Defects in these pathways are known to occur in neurodegenerative diseases which have significant phenotypic overlap with BPAN. To study WDR45's role in these pathways we have made a mouse model with a genetically encoded epitope tag on endogenous WDR45 allowing specific detection of this molecule. This model will be used to explore WDR45's role in the pathways elucidated in the BioID screen and determine the expression pattern of WDR45 in the brain. We have also created a model introducing a patient-analogous premature stop codon early in the WDR45 gene, ablating protein expression and more faithfully recapitulating the human disease phenotype in the mouse. Knowledge of the neurodegenerative progression in these animals and causative mechanisms are key insights allowing for a more informed approach to therapeutic development. These findings reveal previously unexplored functions of WDR45 and potential causatives factors of BPAN pathology.