TMEM106B Loss-of-function dysregulates the pre-synaptic proteome in human iPSC-derived cortical neurons

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TMEM106B haplotypes have been found to modulate the risk for several neurodegenerative diseases such as Frontotemporal lobar degeneration with TDP-43 aggregates and were shown to impact healthy aging and neuronal reserve, suggesting that they determine neuronal vulnerability. These haplotypes are thought to regulate the expression levels of TMEM106B, a lysosomal type-II transmembrane protein, with a slight increase in expression associated with the risk haplotype. However, the mechanisms through which TMEM106B exerts its pathogenicity remain unclear.

We generated full TMEM106B knockout (TMEM106B-/-) iPSC-derived cortical neurons. We performed whole cell mass spectrometry of these neurons at DIV80. We also analyzed lysosomal trafficking with live cell imaging and lysosomal enzymatic activity. In order to have fully mature, spine-bearing neurons, we xenografted neuronal precursor cells in immunodeficient mice and analyzed the cell ramification, spine density and synaptic content of the neurons at 9 months old.

We observed a downregulation of proteins involved in synaptic vesicular metabolism and transport and an upregulation of galectin-3, a marker for lysosomal damage, suggesting alterations of the endolysosomal pathway. We confirmed a significant loss on presynaptic markers and increase on lysosomal markers in the TMEM106B-/- neurons by western blot. Moreover, functional characterization of endolysosomal fitness showed reduced lysosomal trafficking, lysosomal accumulations in the soma and dysregulated cathepsin D activity.

Our results show that loss of TMEM106B leads to a dysregulation of the presynaptic terminal and the endolysosomal system, pointing towards a dysfunction in the recycling or docking of these vesicles. This would indicate a direct role of TMEM106B in the maintenance of healthy presynaptic compartments, and could explain how TMEM106B dysregulations affect neuronal vulnerability.