

Analysing the cell biology of the Parkinson's Disease-linked missense mutation in the retromer VPS35 subunit.

<https://neurodegenerationresearch.eu/survey/analysing-the-cell-biology-of-the-parkinsons-disease-linked-missense-mutation-in-the-retromer-vps35-subunit/>

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Research Abstract

In sorting an array of cargoes, for example proteins, lipids, nutrients, and solutes, to a variety of cellular destinations, the endosomal network performs an essential function in regulating and fine-tuning numerous processes within the cell. Retromer complexes are evolutionarily conserved orchestrators of endosomal sorting. The canonical SNX-BAR-retromer is composed of a stable 'cargo-selective' trimer composed of VPS26, VPS29 and VPS35, and a 'membrane-

deforming sub-complex' composed of a heterodimer of the sorting nexin (SNX)-Bin/Amphiphysin/Rvs (BAR) domain-containing proteins (SNX-BARs) SNX1 or SNX2 with SNX5 or SNX6. The non-canonical SNX3-retromer shares the VPS26:VPS29:VPS35 trimer but contains a distinct membrane-bound sub-complex composed of the non-BAR domain-containing SNX3. These endosomal sorting complexes regulate parallel endosome-to-TGN retrieval pathways and, in the case of the SNX-BAR-retromer, endosome-to-plasma membrane recycling. Recently a missense D620N mutation in VPS35 has been linked with late-onset, autosomal dominant Parkinson's Disease (PD). Although VPS35(D620N) cases show an earlier onset than commonly observed, they are otherwise similar to classic sporadic PD suggestive of considerable overlap in disease pathways. Elucidating not only the VPS35(D620N) mutation but more broadly the role of retromer in neuronal endosomal sorting, may ultimately lead to new insight into the causes of PD. Based on extensive preliminary data we shall test the following hypothesis: The underlying defect for patients with VPS35(D620N)-linked PD is an uncoupling of retromer-mediated cargo sorting from WASH-dependent actin polymerization, which is manifested as a decrease in the efficiency of processing of tubular profiles into isolated transport carriers, and a resultant defect in retromer-mediated endosomal sorting of neuronal cargo proteins, that include specific glucose transporters that normally function to suppress PD neuropathology.

Further information available at:

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