

P023 Frontotemporal dementia-causing *CHMP2B* mutants produce an enlarged endosomal phenotype and alter growth factor trafficking

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A splice site mutation in the ESCRT-III component *CHMP2B* is likely to be responsible for causing frontotemporal dementia in a large Danish family termed frontotemporal dementia linked to chromosome 3 or FTD-3. The splice site mutation leads to the formation of two C-terminally truncated transcripts termed *CHMP2B*^{Intron5} and *CHMP2B*^{Δ10}. Over-expression of the mutant proteins encoded by these transcripts in human neuroblastoma cell lines SK-N-SH or SH-SY-5Y leads to the formation of enlarged aberrant late endosomes which show colocalisation with ubiquitin. An enlarged endosomal phenotype was also found in fibroblast cell lines derived from affected FTD-3 family members, confirming these findings in patient tissue. SK-N-SH cells over-expressing *CHMP2B* mutant proteins also show impaired degradation of epidermal growth factor. Deregulation of growth factor trafficking may cause impaired trophic support and/or aberrant cellular signalling. These data suggest that mutations in *CHMP2B* may alter endosomal trafficking, adding to the growing body of evidence that impaired endosomal function has a critical role in neurodegenerative disease.