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Deficiency of *GRN*, a frontotemporal dementia gene, results in gangliosidosis

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Haploinsufficiency of *GRN* causes frontotemporal dementia (FTD). The *GRN* locus produces progranulin (PGRN), a precursor protein that is cleaved to lysosomal granulin polypeptides. The function of lysosomal granulins and why their absence causes neurodegeneration are unclear. Here we investigated PGRN function in lysosomal lipid degradation and discovered that PGRN-knockout human cells, PGRN-deficient murine brain, and frontal lobes of human brains from patients with *GRN* mutation-related FTD have increased levels of gangliosides (abundant sialic acid–containing glycosphingolipids). The levels and activities of lysosomal enzymes that catabolize gangliosides were normal, but levels of bis(monoacylglycero)phosphate (BMP), a lipid required for ganglioside catabolism, were reduced in PGRN-deficient cells and patient brain tissues. Our findings suggest that lysosomal granulins are required to maintain BMP levels to support ganglioside catabolism and that PGRN deficiency in lysosomes leads to gangliosidosis. Lysosomal ganglioside accumulation may contribute to neuroinflammation and neurodegeneration susceptibility of PGRN deficiency and other neurodegenerative diseases.

Conflicts of interest

I am now an employee of Prevail Therapeutics/Eli Lilly. The work presented here was conducted prior to my employment at Prevail Therapeutics.
Therefore, the data and conclusions expressed in this abstract are those of the authors and do not necessarily reflect the views or positions of Prevail Therapeutics.