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Thursday

Investigation of the impact of reduced levels of progranulin in mice and patient-derived cells

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Frontotemporal lobar degeneration (FTLD) is a common type of dementia that encompasses a group of neurodegenerative disorders that cause selective atrophy of the frontal and temporal lobes of the brain. A major cause of FTLD with TAR DNA-binding protein-43 (TARDBP/TDP-43) positive inclusions is *GRN*haploinsufficiency causing decreased levels of its gene product progranulin. The role of progranulin in the CNS remains to be elucidated but *GRN* loss-of-function (LOF) carriers are characterized by significantly reduced progranulin levels in plasma and CSF, which has led to the hypothesis that elevating progranulin levels could be a therapeutic strategy in FTLD. Intriguingly, individuals carrying two LOF alleles in *GRN* present neuronal ceroid lipofuscinosis, a lysosomal storage disorder. Further, several recent studies converge on the finding that progranulin and its processed forms (granulins) play a critical role in lysosomal function. To develop preclinical models for the progranulin pathway, we have studied the biochemical phenotypes in neurons and cortical homogenates from *Grn* heterozygous (+/-) mice, as well as fibroblasts from *GRN* LOF carriers. Both models showed around 50% reduction in granulins but only minor changes in a range of lysosomal markers. Furthermore, cultured cortical neurons from *Grn* (+/-) mice showed normal survival. Interestingly, RNAseq of the cortical transcriptome revealed significant changes in several genes of interest in aged *Grn* (+/-) mice compared to wild-type littermates. Taken together, our findings suggest that despite some biochemical changes, *Grn* (+/-) mice and patient-derived cells from *GRN* haploinsufficiency only display a subtle phenotype.

Conflicts of interest

N/A