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Conserved astroglial toxicity promotes synaptic degeneration in frontotemporal dementia with *GRN* mutations

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Mutations in the human *Progranulin* (*GRN*) gene are a leading cause of frontotemporal lobar degeneration (FTLD). While previous studies implicate aberrant microglial activation as a disease-driving factor in neurodegeneration in the thalamocortical circuit in *Grn*-/- mice, the exact mechanism for neurodegeneration in FTLD-*GRN* remains unclear. By performing comparative single-cell transcriptomics in the thalamus and frontal cortex of *Grn*-/- mice and patients with FTLD-*GRN*, we have uncovered a highly conserved astroglial pathology characterized by upregulation of gap junction protein GJA1, water channel AQP4, and lipid-binding protein APOE, and downregulation of glutamate transporter SLC1A2, that promotes profound synaptic degeneration across the two species. This astroglial toxicity can be recapitulated in mouse astrocyte-neuron cocultures and by transplanting human induced pluripotent stem cell-derived astrocytes to cortical organoids, where Progranulin-deficient astrocytes promote synaptic degeneration, neuronal stress, and TDP-43 proteinopathy. Together, these results reveal previously unappreciated astroglial pathology as a key mechanism in neurodegeneration in FTLD-*GRN*.

Conflicts of interest

A.R.K. is a founding member of Neurona Therapeutics. All other authors declare no conflicts of interest.