and subsets of brain vascular endothelial cells. Phospho-tau positive dystrophic neurites were associated with PGRN structures, but we did not observe PGRN positive neurofibrillary tangles. There was significant increase in PGRN protein levels in AD compared to LP and HP cases by western blot, with significant correlation between PGRN and tangle scores but not plaque scores. In 2/3 FTLD cases, PGRN-positive microglia were observed, particularly in white matter. **Conclusions:** The role of PGRN in AD is still unclear as levels are increased. Activated microglia have increased amounts of anti-inflammatory PGRN, and most Aβ plaques are PGRN-positive. The consequence of early deposits of PGRN on Aβ plaques asks the question whether PGRN is promoting the formation of plaques or aiding in their removal by microglia.

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**P1-186** IMPAIRED β-GLUCOCEREBROSIDASE ACTIVITY AND PROCESSING IN FRONTOTEMPORAL DEMENTIA DUE TO PROGRANULIN MUTATIONS

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**Background:** Loss-of-function mutations in progranulin (GRN) are a major autosomal dominant cause of frontotemporal dementia (FTD). Progranulin is critical for lysosomal function, as individuals with loss-of-function mutations on both GRN alleles develop the lysosomal storage disorder Neuronal Cereoid Lipofuscinosis.Brains from FTD patients with GRN mutations (FTD-GRN) exhibit accumulation of lysosomal proteins and lysosomal storage material, indicating that lysosomal dysfunction may be a key driver of FTD-GRN pathogenesis. Progranulin’s role in maintaining lysosomal function remains incompletely understood, though recent data indicate that progranulin may regulate the maturation and trafficking of lysosomal enzymes. Additionally, progranulin interacts with prosaposin, a key co-factor for enzymes that metabolize glycosphingolipids (GLSs).

**Methods:** To investigate progranulin’s role in the lysosome, we assayed the activity of GSL-metabolizing enzymes in frontal cortex from progranulin-insufficient mice and inferior frontal gyrus of FTD-GRN patients (n=7) and controls (n=5). We also studied patients with Alzheimer’s disease (AD) (n=10) as a neurodegenerative comparison group. Enzyme levels and post-translational modifications were assessed by western blot.

**Results:** We observed elevated activity of β-galactosidase, β-glucosaminidase, and α-galactosidase, but impaired β-glucocerebrosidase (GCase) activity in brains from 7–10 month-old Grn−/− mice. Similar to Grn−/− mice, GCase activity was impaired in FTD-GRN patients, but not AD patients. The GCase activity deficit in FTD-GRN patients was associated with lower levels of mature, glycosylated GCase. Immunoblot of most of the FTD-GRN and AD brains revealed a lower-molecular weight, incompletely glycosylated form of GCase that accumulated in the sarkosyl-insoluble fraction. FTD-GRN brains also exhibited higher levels of apparently ubiquitinated GCase. These data are consistent with impaired processing of GCase. Using immunopre-

cipitation and proximity ligation assays, we found that progranulin interacts with GCase. Additionally, restoration of progranulin to Grn−/− mice with an AAV vector normalized GCase activity.

**Conclusions:** These data show that brains from FTD-GRN patients have impaired GCase activity, which may be due to impaired GCase processing. This may be a direct result of progranulin insufficiency, as progranulin interacts with GCase, and Grn−/− mice exhibit similar deficits as FTD-GRN patients that are normalized by restoring progranulin.