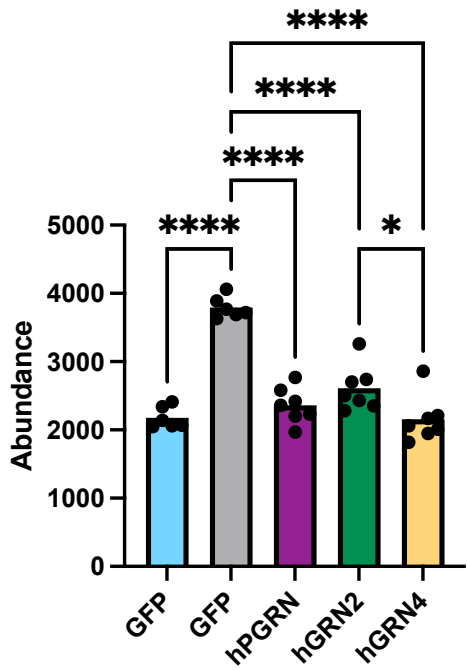
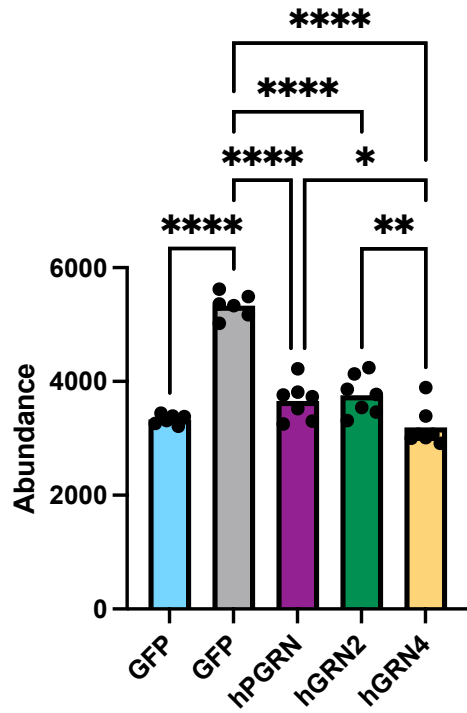


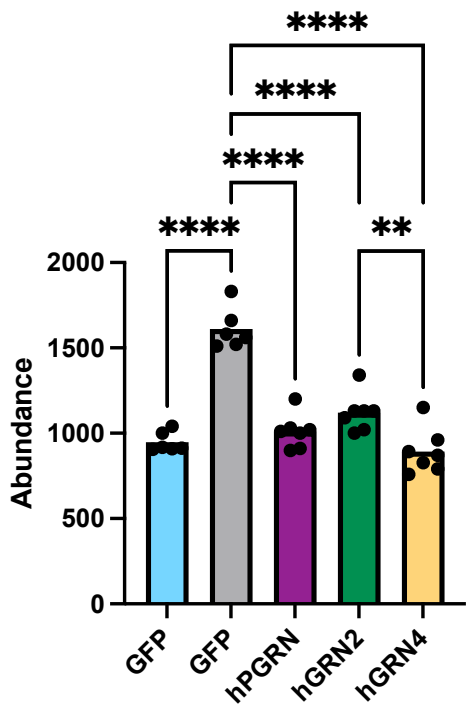
C1qa



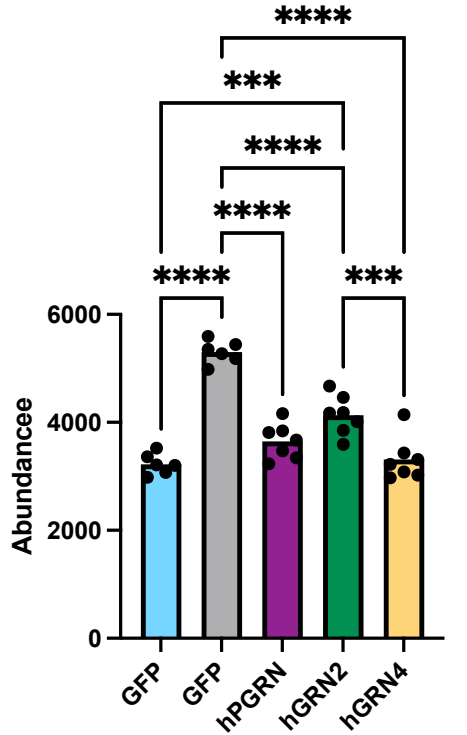
C1qb

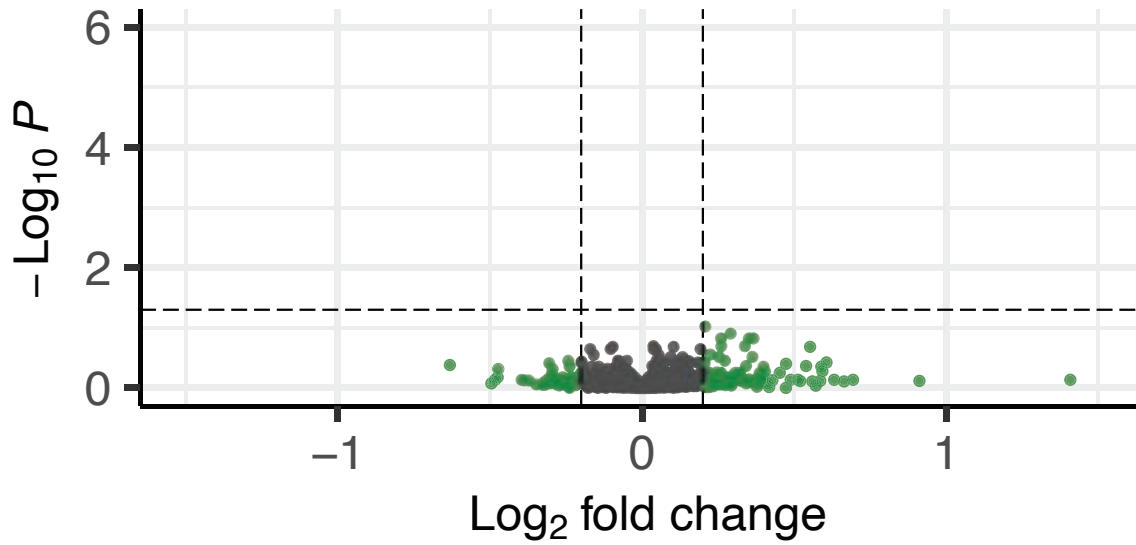
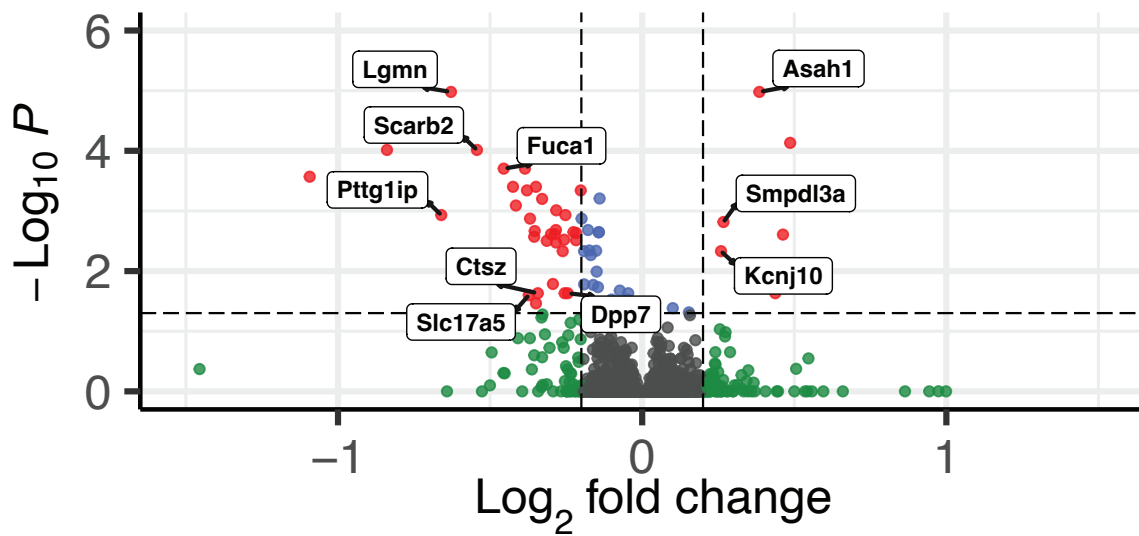


C1qc



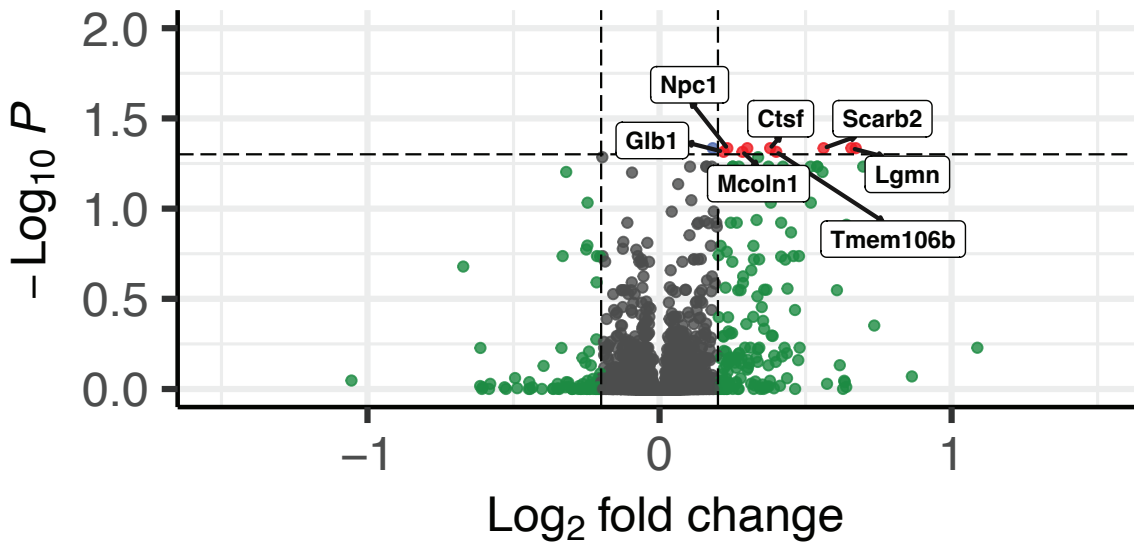
C4B



PGRN vs hGRN4● NS ● Log₂ FC**hPGRN vs hGRN2**● NS ● Log₂ FC ● p-value ● p-value and log₂ FC

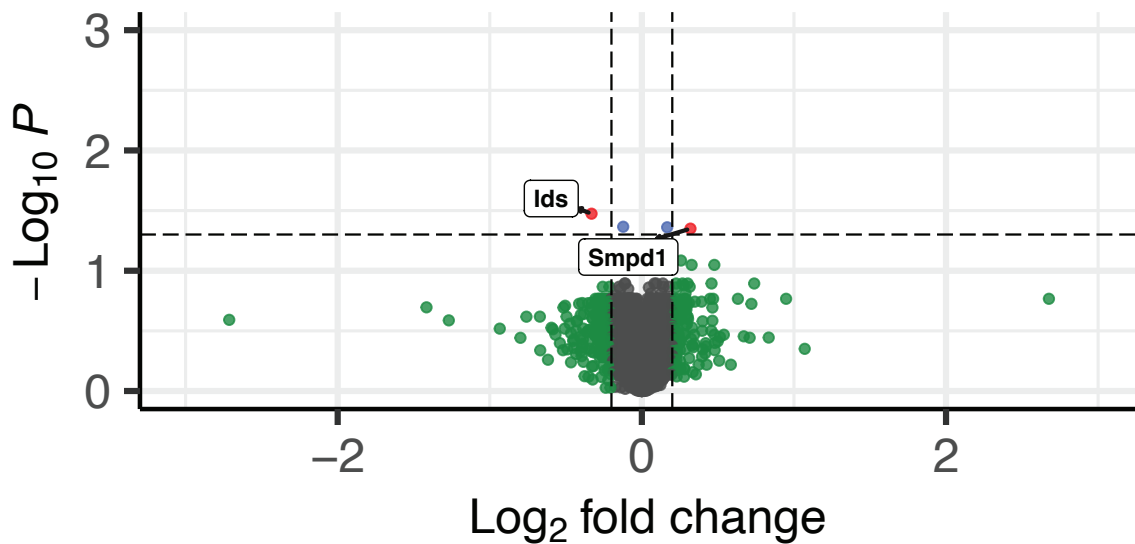
GRN2 vs hGRN4

● NS ● Log_2 FC ● p-value ● p-value and log_2



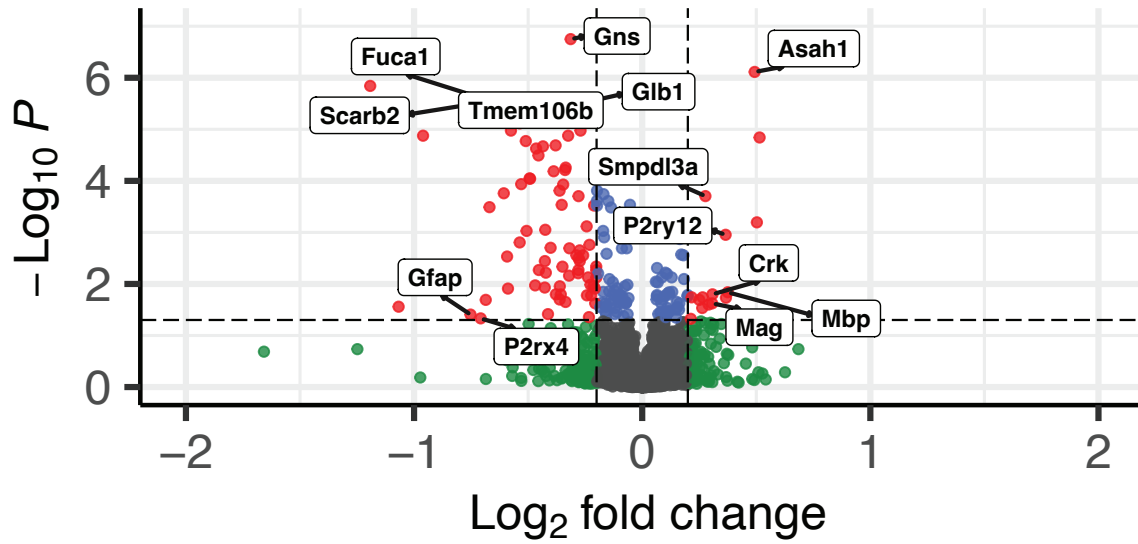
WT vs hGRN4

● NS ● Log_2 FC ● p-value ● p-value and log_2 FC



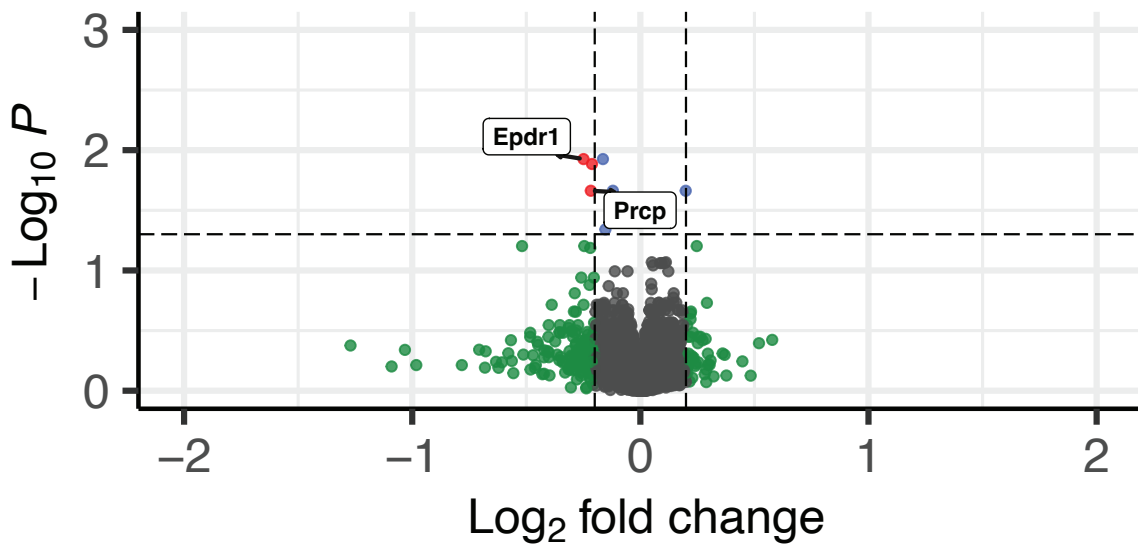
WT vs hGRN2

● NS ● Log₂ FC ● p-value ● p-value and log₂ FC

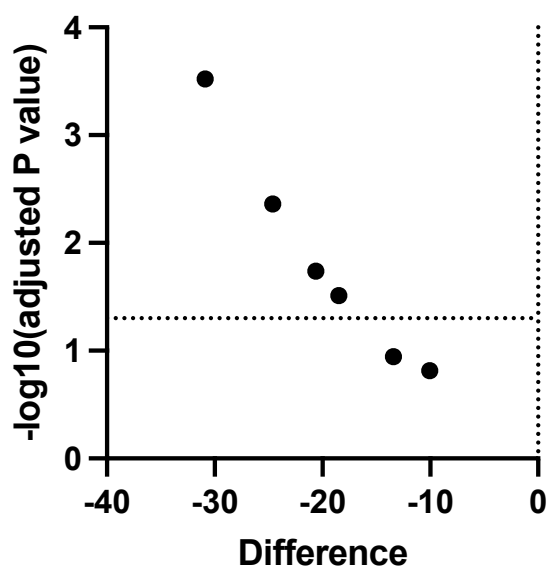


WT vs hPGRN

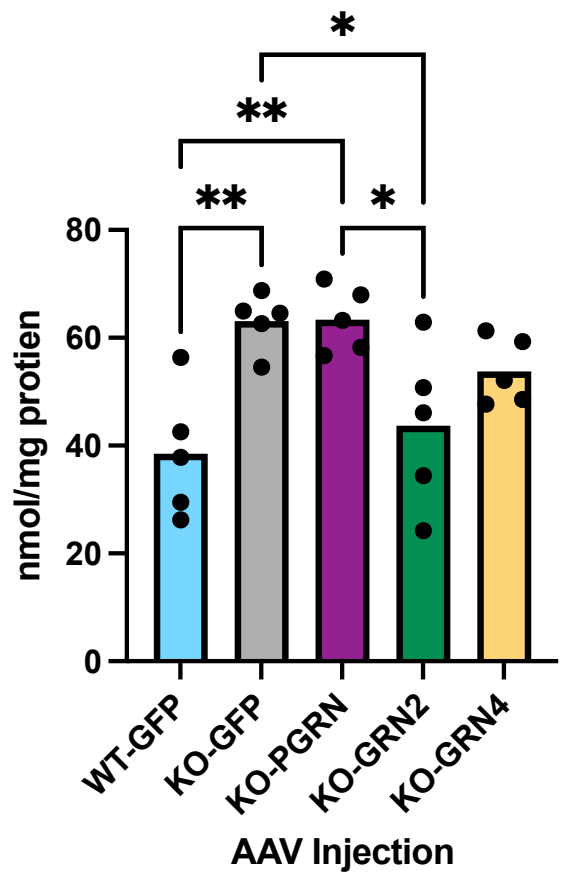
● NS ● Log₂ FC ● p-value ● p-value and log₂ FC



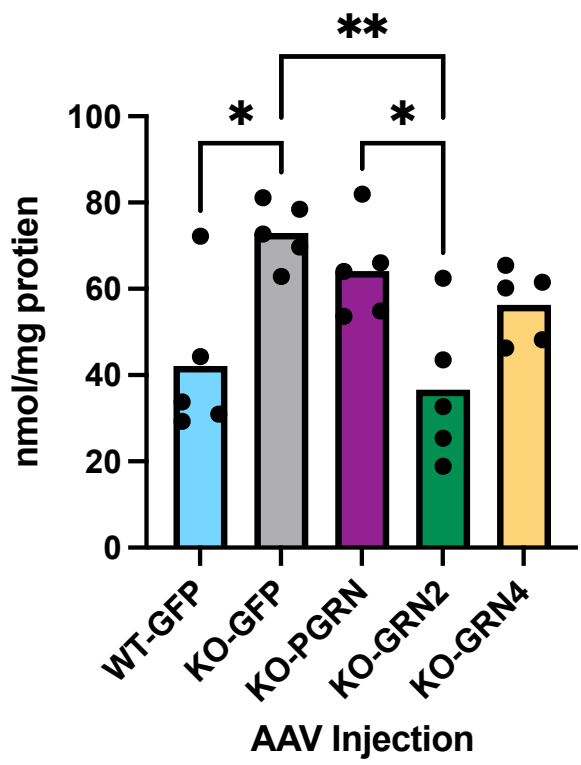
LCL -log10(adjusted P value)



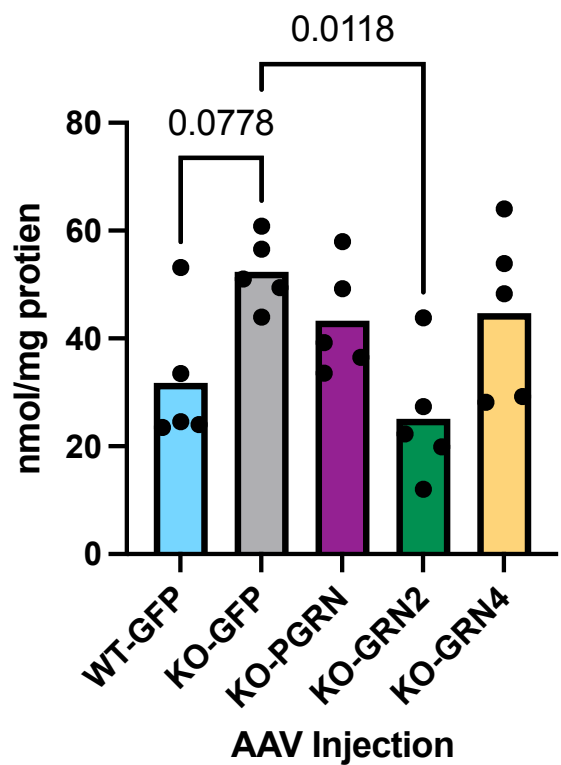
LCL 18:1-18:1-18:1

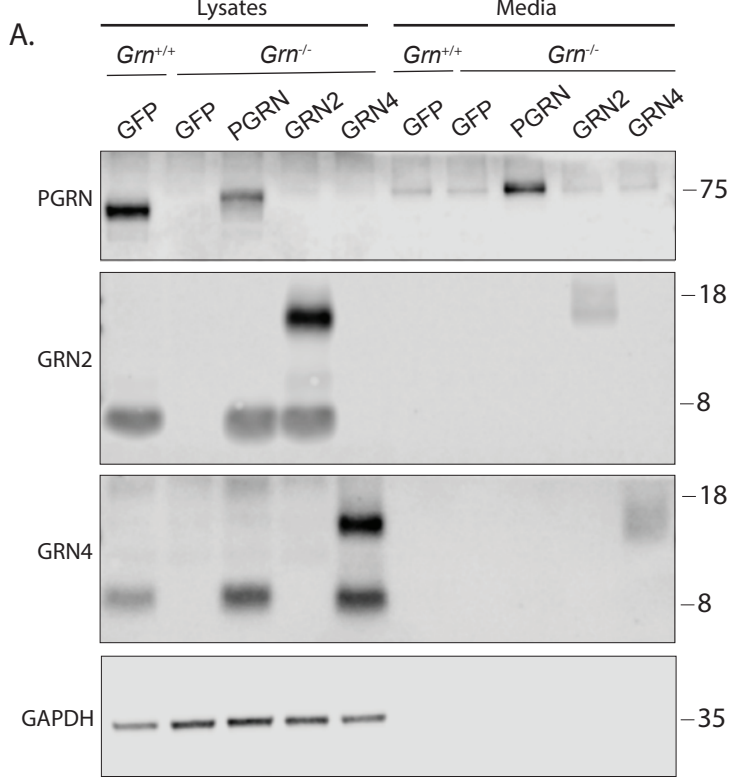


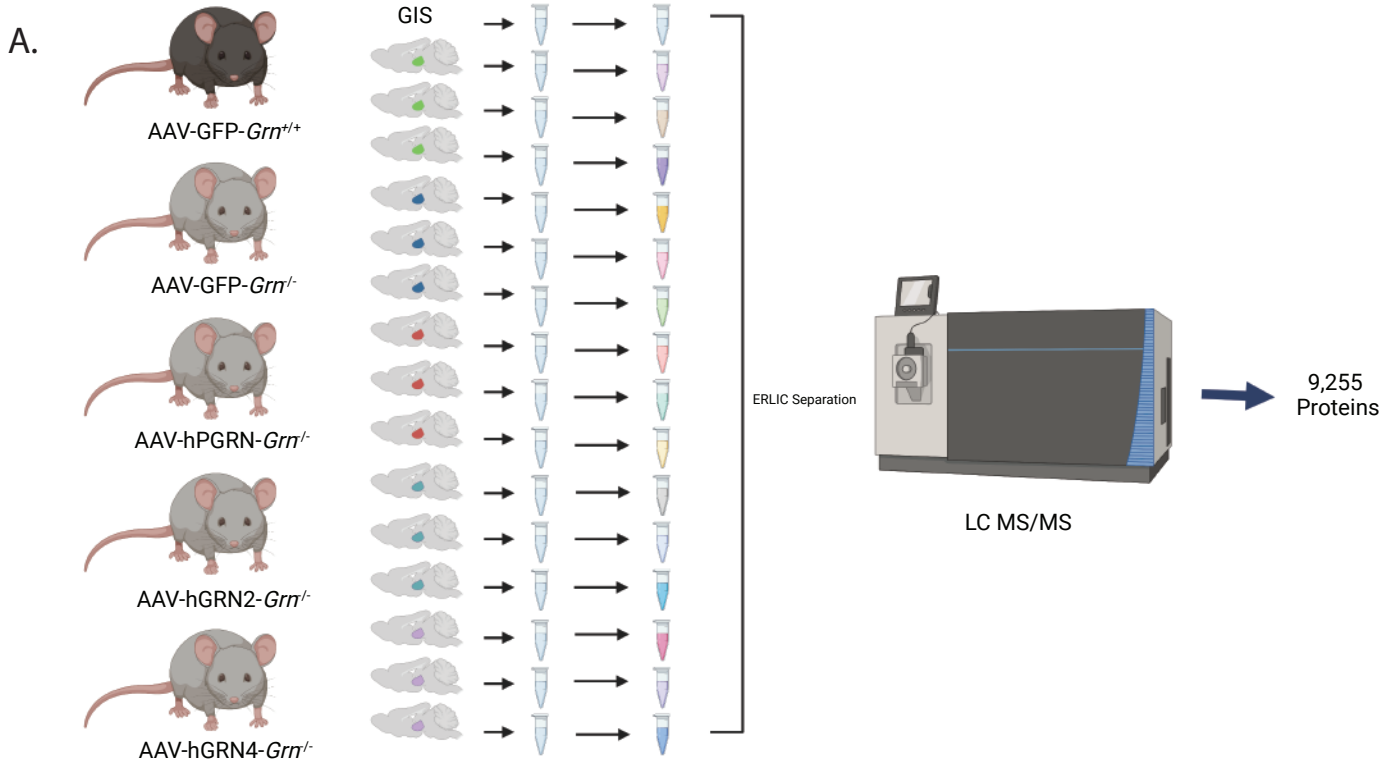
"LCL 18:2-18:2-20:2/18:2-18:1-20:3 (1:1)"



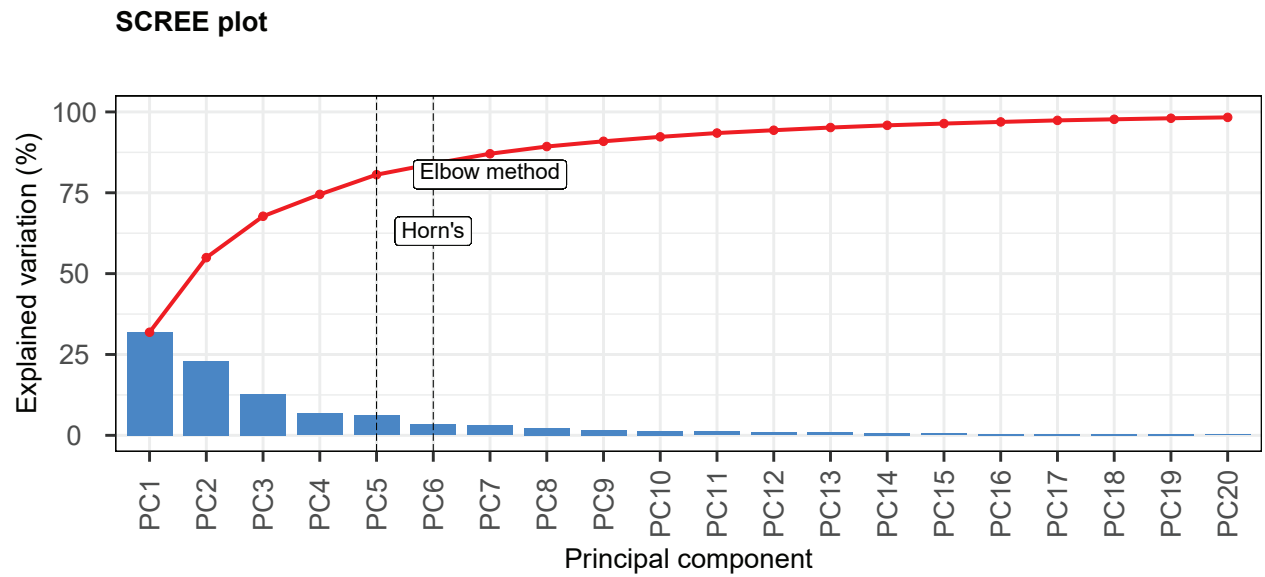
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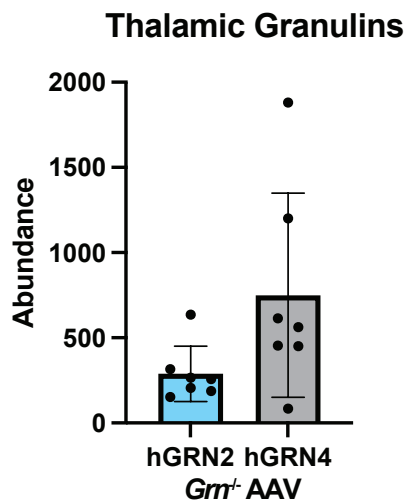




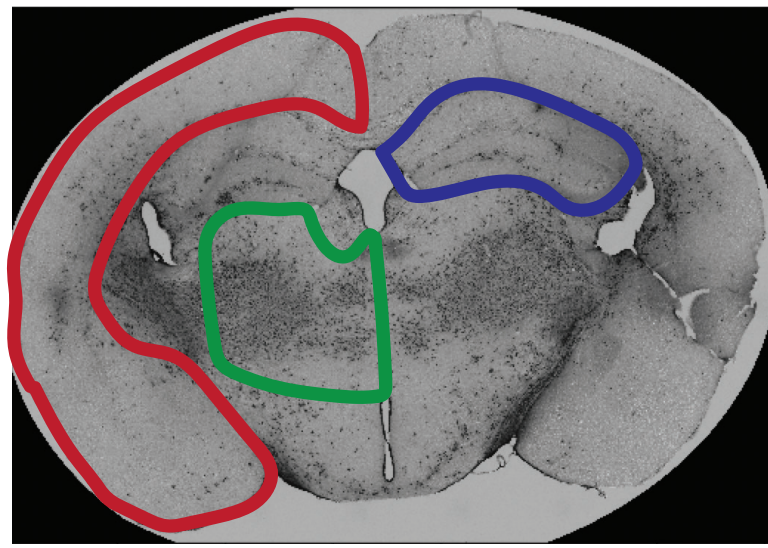
B.



C.



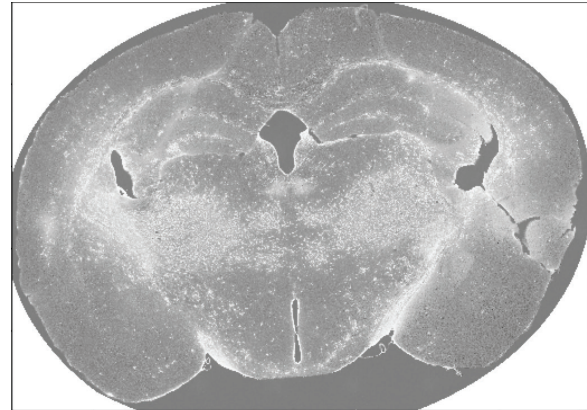
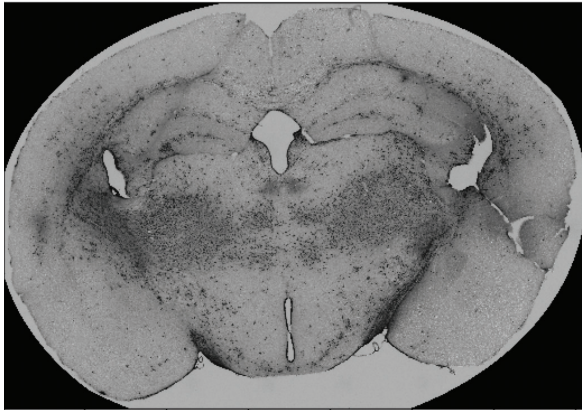
A.



Input Image

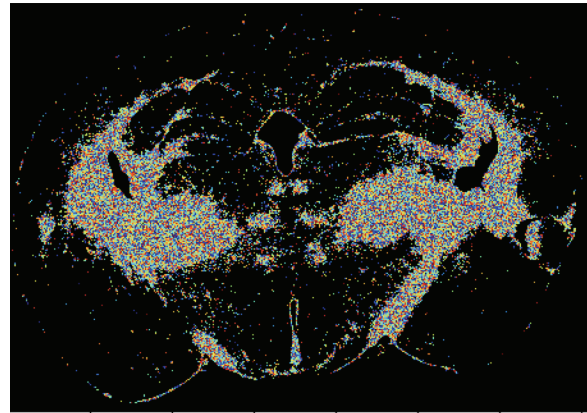
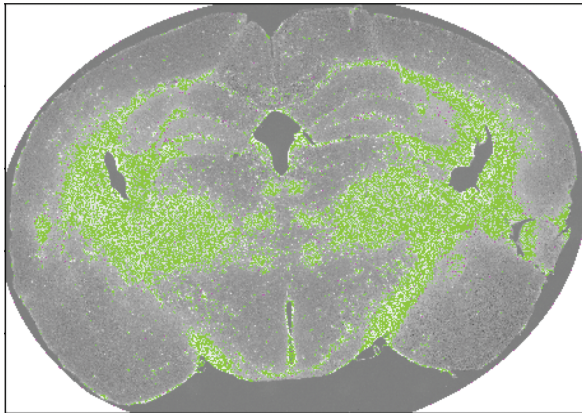
Inverse Image from DAB

B.



Signal Outlines

Signal Area



Legends Appendix 4

SUPPLEMENTAL FIGURE TITLES AND LEGENDS

Supplemental Figure 1: Granulin Peptide Alignments and PID

- A. ClustalW alignment of Human granulin sequences. Visualized using ggmsa R package. Amino acids are color coded by their chemical properties.
- B. Percent Identity heatmap derived from PID values calculated using granulin alignment output from figure S1A. Visualized using the Bio3D R package.

Supplemental Figure 2: Validation that hPGRN, hGRN2, and hGRN4 are properly trafficked to the lysosome and secreted.

- A) Immunoblot of cell lysate and conditioned media collected from HeLa wild-type or *Grn*^{-/-} cells expressing hPGRN, hGRN2, or hGRN4. Probed for hPGRN, hGRN2 and hGRN4.

Supplemental Figure 3: Thalamic Proteomics

- A) Diagram of the proteomic thalamic workflow, displaying the number of proteins detected 9,255.
- B) Assessment of Horn's Parallel Analysis to determine how many components from the PCA to retain in downstream consideration.
- C) Welch's T-test comparing the abundance of granulin peptide detected in hGRN2-*Grn*^{-/-} and hGRN4-*Grn*^{-/-} mice thalamus (p-value=0.091) mean hGRN2= 288.4 mean hGRN4= 749.3

Supplemental Figure 4: Cell Profiler Workflow

- A) Example of cropped ROIs from whole coronal section images. Bilateral images were collected from each section for each region.
- B) Overview of CellProfiler workflow and output. Signal Area represents the regions quantified by pipeline.