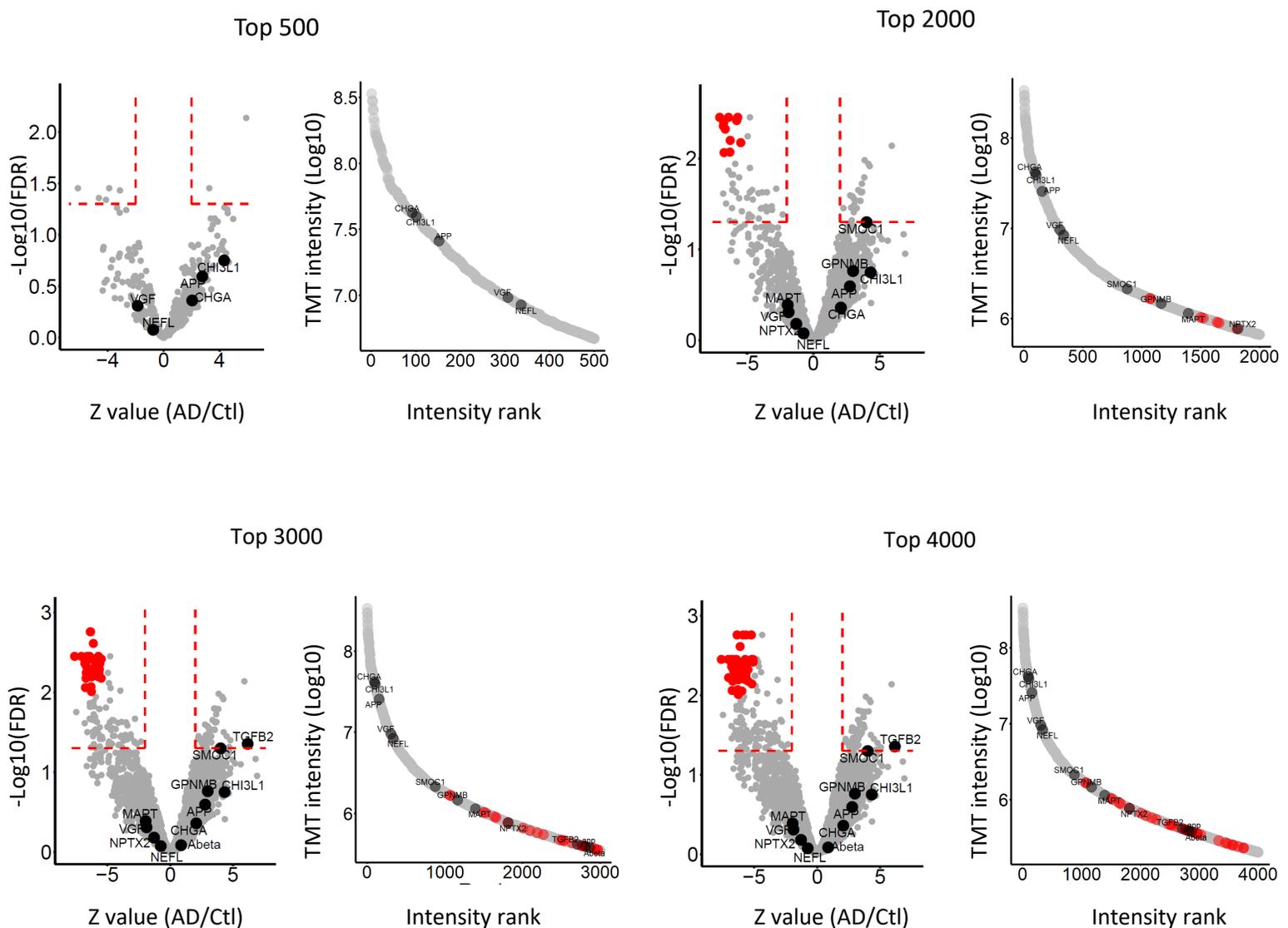


Supplementary Figure 1: Majority of top differentially expressed (DE) mitochondrial proteins are tightly correlated with each other in the cerebrospinal fluid (CSF)

Pairwise Pearson correlation analysis was performed for the top DE mitochondrial proteins.

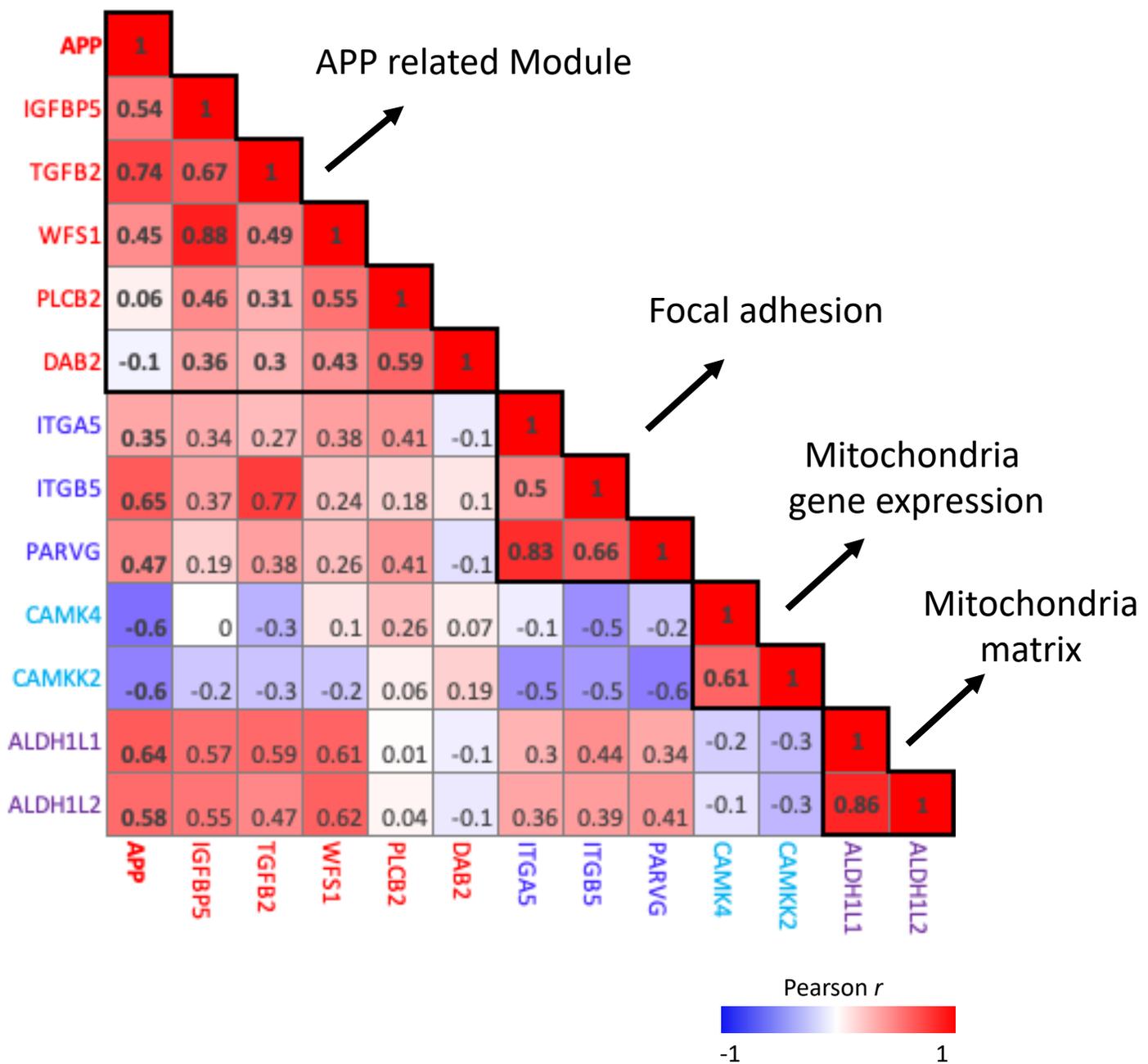
Heatmap shows the Pearson correlation coefficient (r) values of top DE mitochondrial proteins.



Supplementary Figure 2: Ultra-deep profiling depth is a prerequisite to detect evident mitochondrial signatures presented in AD CSF proteome

Volcano plots and corresponding scatter plots of the top 500, 2000, 3000, 4000 most abundant proteins.

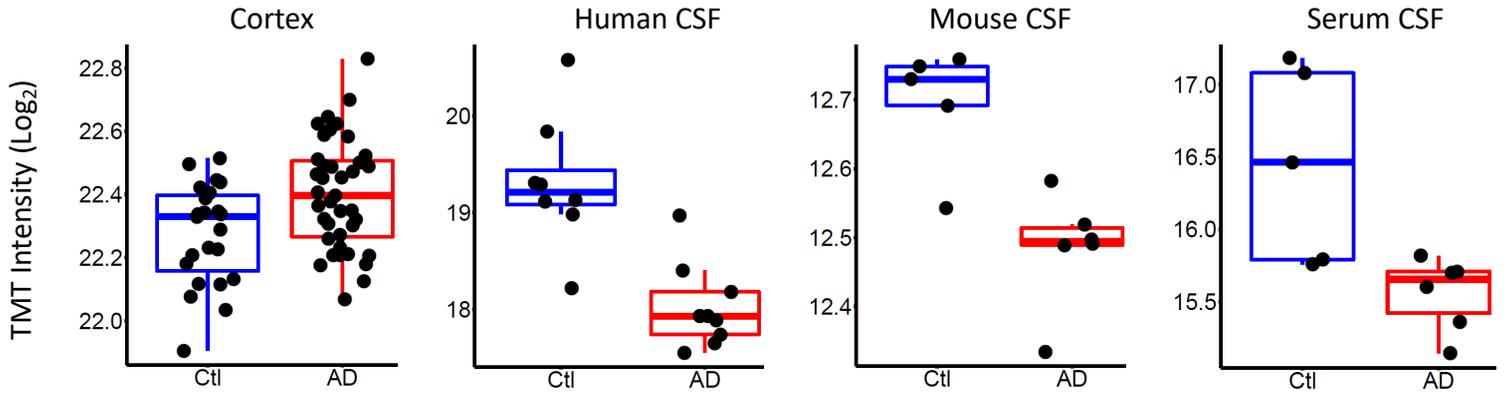
For the volcano plots, X-axis shows the Z value of the Z score transformed \log_2 level fold changes comparing AD to Ctl. Y-axis shows the $-\log_{10}$ level FDR value. Previously reported AD CSF biomarkers are plotted in black and labeled. Top DE mitochondrial proteins with $FDR < 0.01$ and $Z \text{ value} < -5$ are plotted in red. For the scatter plots, CSF proteins are plotted as a function of their concentration rank (x-axis) and their mean \log_{10} level TMT intensity in all samples (y-axis). Previously reported AD CSF biomarkers are plotted in black. Top DE mitochondrial proteins with Z score difference > 5 and $FDR < 0.01$ were plotted in red.



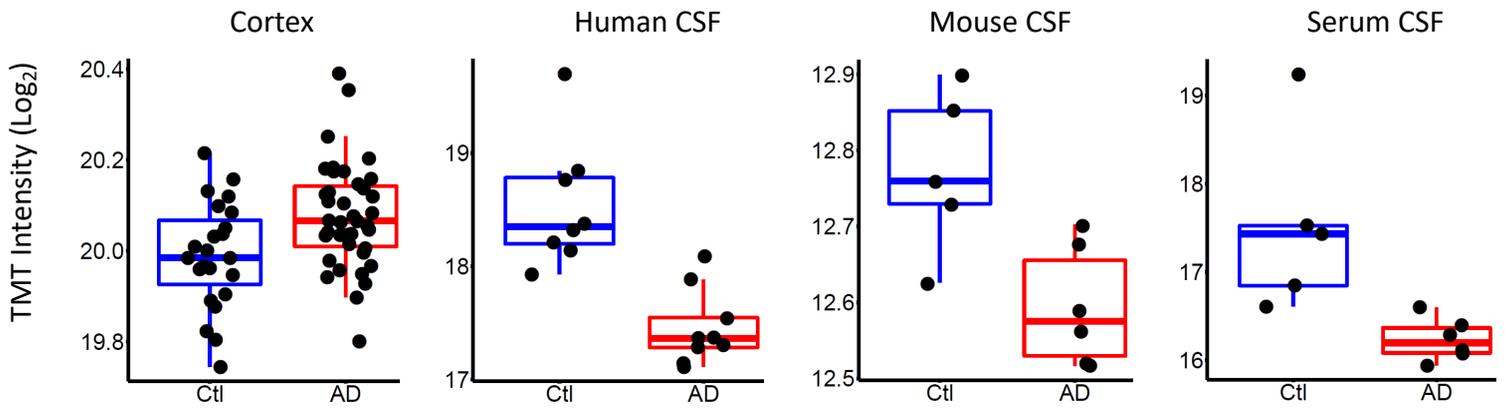
Supplementary Figure 3: PPI module proteins are highly correlated with each other

Heatmap shows pairwise correlation analysis of PPI proteins detected in Figure 3E. Pearson correlation coefficient r values of each pairwise correlation analysis in the cortex are displayed. The color of each module matches the PPI module edge colors in Figure 3E.

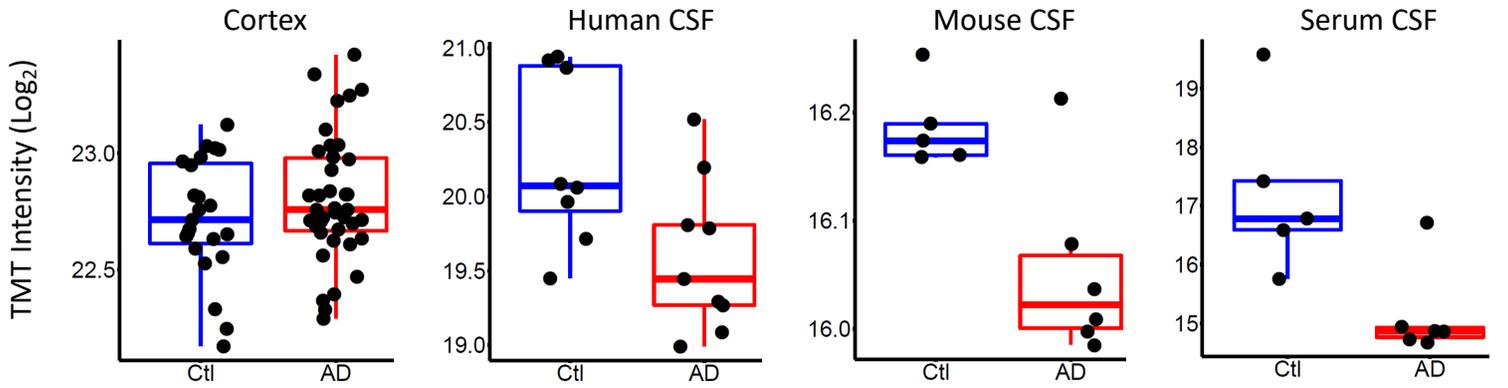
ALDH6A1



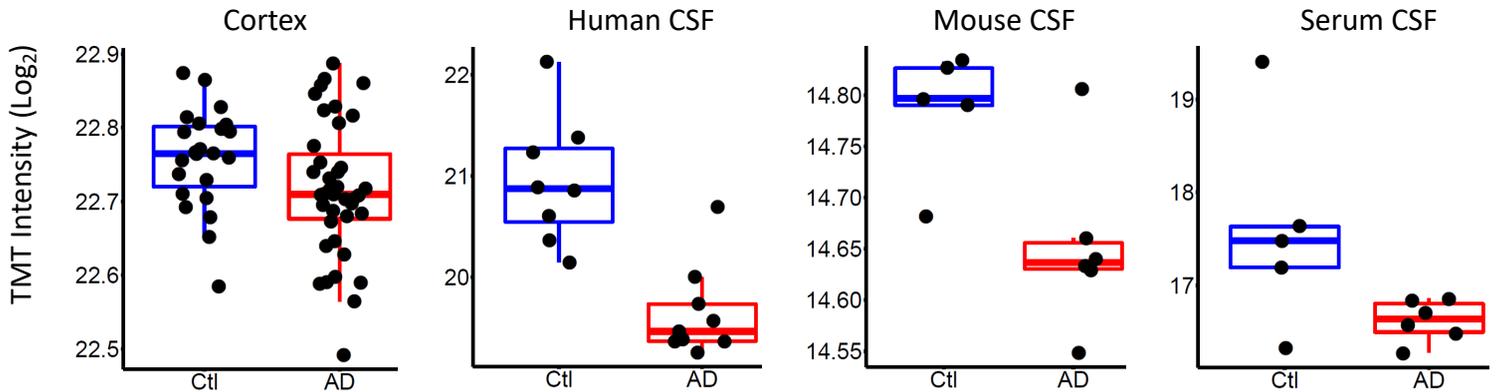
ETFB



SOD2



PRDX3



Supplementary Figure 4: Mitochondrial proteins that have decreased expression levels in AD in all three analyzed biofluids

Dot plots overlaid onto boxplots showing expression of proteins in human cortex, human CSF, mouse CSF and serum. X-axis shows sample groups, y-axis indicates Log_2 transformed TMT intensity. Boxplot center line, median; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; points, expression levels of each individual samples.