Supplemental Figure Legends:

Fig. S1. Protein and liquid-chromatography quality control measures. Related to Star Methods (A) Coomassie-stained SDS-PAGE of BLSA frontal cortex (FC) and precuneus (PC) homogenates in 8M urea (10 µg per lane) show little difference in general proteome integrity. (B) Reverse phase nanoscale liquid chromatography of 2 µg trypsin digested total brain homogenate containing isotopically labeled peptide standards. Upper panel, base peak chromatogram of all MS peaks; lower panel, extracted ion intensities for 15 spiked-in isotopically labeled heterologous retention time standards elute throughout the reverse phase gradient and provide marks for consistency and alignment of all peaks. **(C)** Retention time consistency of 14 out of the 15 standard peptides was measured across the 47 FC homogenate runs and graphed as a box plot. Peptide sequences are inset. **(D)** Run-to-run drift of overall relative intensity of the geometric mean of the signal for the 1000 most intense proteins across the 47 FC samples, measured three ways: as simple summed peptide intensity (red trace), as summed intensity corrected for drift in intensity of equally spiked-in peptide retention time standards (blue trace), and as the MaxLFQ algorithm output for delayed normalization of protein LFQ intensity of the same 1000 proteins (green trace). MaxLFQ showed the least variation in signal intensity.

Fig. S2. Peptide intensity of four different representative peptides of APP assessed by disease status. Related to Figure 1. Top left panel, APP Kunitz protease inhibitor (KPI) domain peptide (WYFDVTEGK, residues 307-315 in APP_{770}) was detected at low levels without change across different status groups in total homogenate by LC-MS/MS. Top right panel, an N-terminal peptide from APP_{695} (THPHFVIPYR, residues 107-116 in APP_{695}) was also found with about 5-fold more intensity but also at monotonic levels across status groups. In contrast, consecutive Aβ peptides

HDSGYEVHHQK and LVFFAEDVGSNK were detected with intensities an order of magnitude higher, with significant elevation in AsymAD, and AD cases in the BLSA frontal cortex (bottom two panels).

Fig. S3. Differential expression analysis in BLSA precuneus (PC) and frontal cortex (FC). Related to Figure 1. (A) Venn diagrams of differentially expressed proteins in either the PC or FC across three comparisons (i) controls vs. AsymAD (ii) controls vs. AD and (iii) AsymAD vs. AD samples. (B) Gene ontologies significantly increased (n=55) or decreased (n=67) in two of the three aforementioned comparisons in either brain region (i.e., two or more of six comparisons).

Fig. S4. Differential expression analysis across Emory and BLSA frontal cortex. Related to Figure 1. (A) Correlation of overlapping significantly and specifically changed AD proteins (ANOVA $p<0.05$) in the Emory (*x-axis*) and BLSA *(y-axis*) cohorts in dorsolateral prefrontal cortex including Aβ. A Pearson correlation coefficient (cor) of 0.97 was observed (p=6.7e-30). (B) Proteomic quantification of heat shock protein, HSP27 (HSPB1) in the Emory and BLSA cases. (C) Western blot analysis of HSPB1 in a subset of Emory cases (control, AD, PD and ALS) confirmed HSPB1 specificity in AD. TDP-43 was used as a loading control, which showed no difference between groups (lower panel). (D) Quantification of HSPB1 by densitometry. (*, $p<0.05$; **, $p<0.01$; *** $p<0.001$, ANOVA with Tukey's post hoc test).

Fig. S5. Additional Emory protein networks. **Related to Figure 4.** (A) Five additional Emory modules that overlap with BLSA. (B) Six Emory modules do not overlap with BLSA. Significance of all eigenprotein changes was measured using Kruskal-Wallis ANOVA p-values. Box plots with error bars beyond the 25^{th} and 75^{th} percentiles are displayed for each of the four groups (control,

PD, ALS and AD) in module boxplots. Outlier cases are shown as unfilled circles beyond the error bars.

Fig. S6. Emory modules GWAS enrichment. **Related to Figure 6.** AD GWAS candidate genes were enriched in E-M2 (25 genes including BIN1 and PICALM) and E-M3 (12 genes including APOE and CLU), modules that are enriched with oligodendrocyte and microglial/astrocyte markers. GWAS candidate genes from Autism Spectrum Disorder (ASD) and schizophrenia were predominately over-represented in neuronal modules. Random sampling (10,000 times) of the MAGMA gene list was used to assess the significance of the module enrichment score (* p value <0.05).

Supplemental Table Legends:

Table S1. BLSA Case Information. Related to Star Methods

Table S2. BLSA Differential and Co-expression Protein Analysis. Related to Figure 1 and 2.

Table S3. Gene Ontology (GO) Term enrichment for proteins in BLSA network. Related to Figure 2.

Table S4. Cell type-specific marker lists used to identify cell type enrichment in protein and RNA modules. Related to Figure 2 and 5.

Table S5. Emory Case Information. Related to Star Methods

Table S6. Emory Differential and Co-expression analysis. Related to Figure 4, 5 and 6.

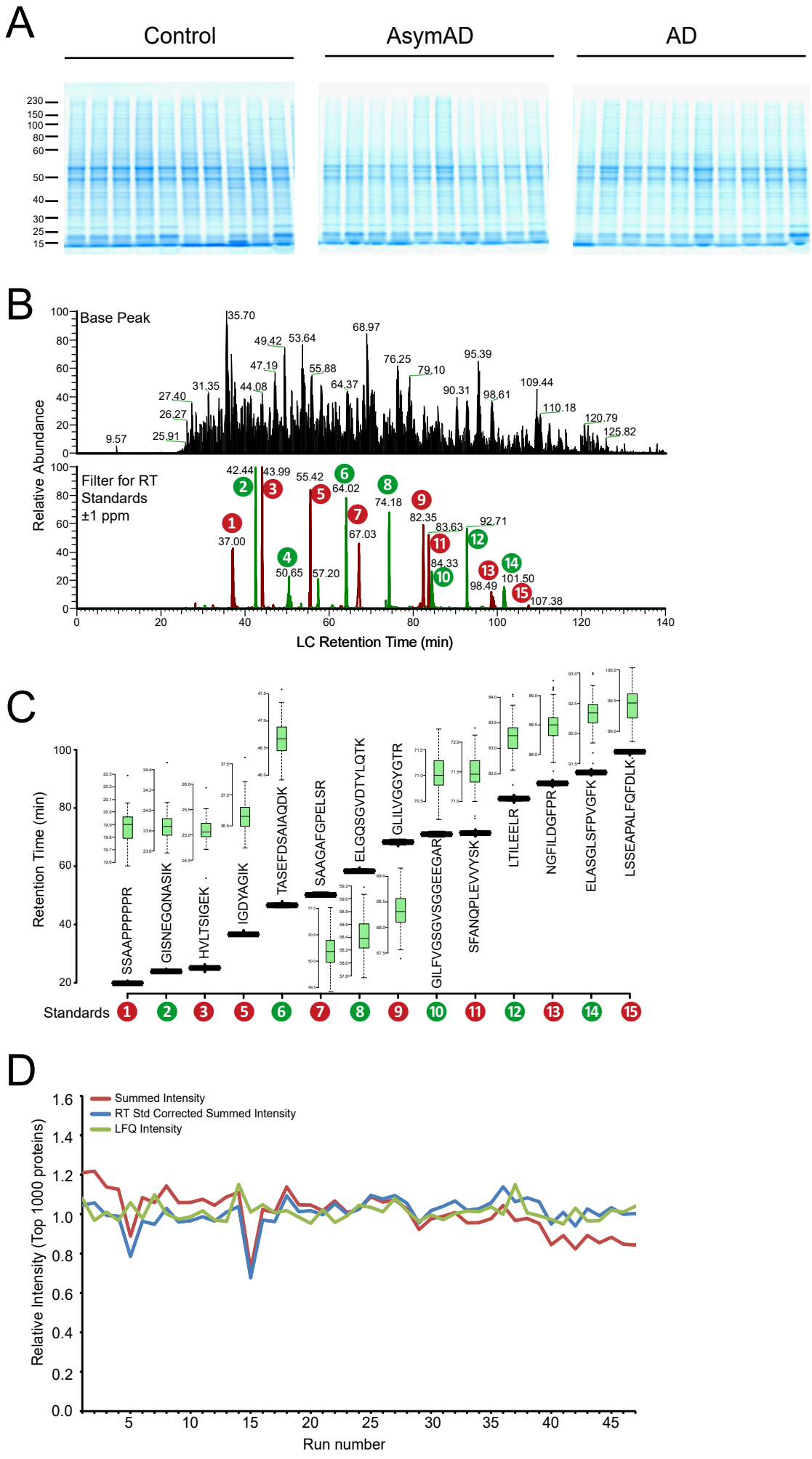
Table S7. Gene Ontology (GO) term enrichment for proteins in Emory network. Related to Figure 4.

Table S8. RNA and co-expression analysis and module membership. Related to Figure 5 and 6.

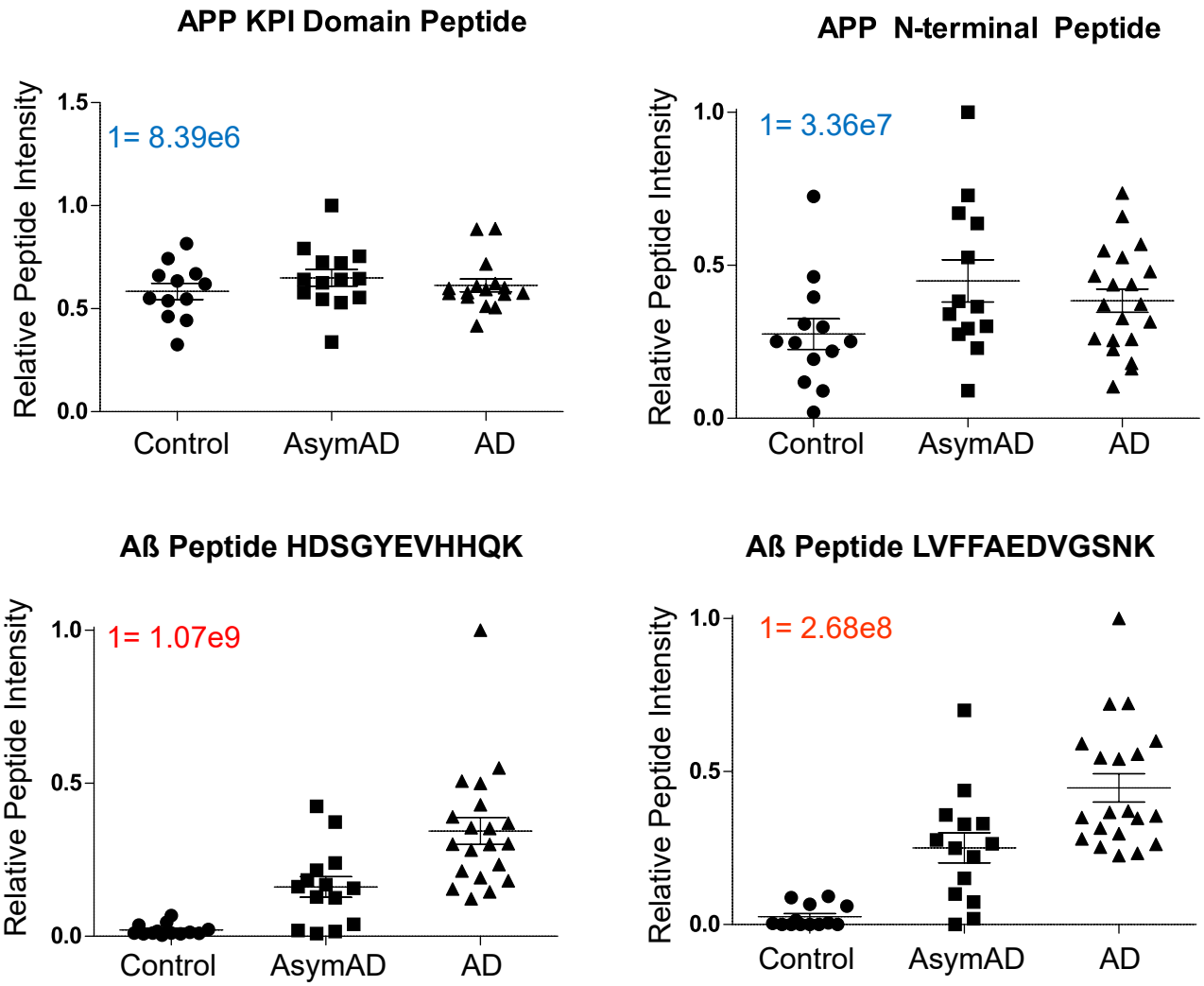
Table S9. Gene Ontology (GO) term enrichment for transcriptome network. Related to Figure 5.

Table S10. MAGMA GWAS significance for specific genes associated to AD, autism spectrum disorders (ASD), or schizophrenia single nucleotide polymorphisms. Related to Figure 6

Supplemental Figure 1

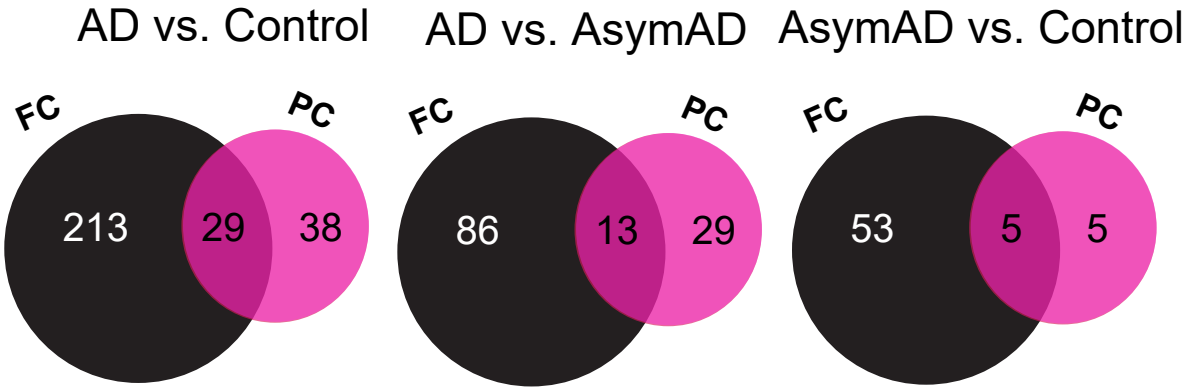


Supplemental Figure 2



Supplemental Figure 3

A



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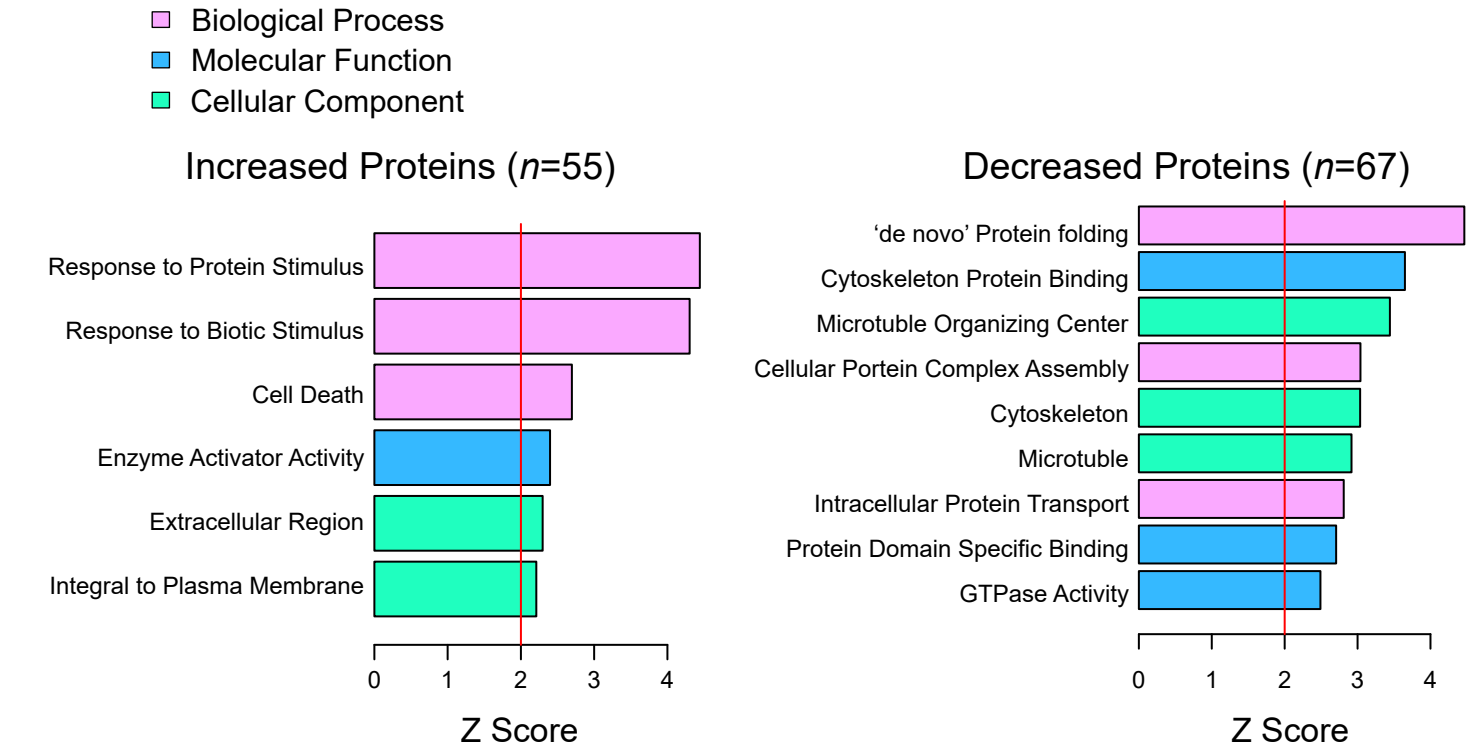

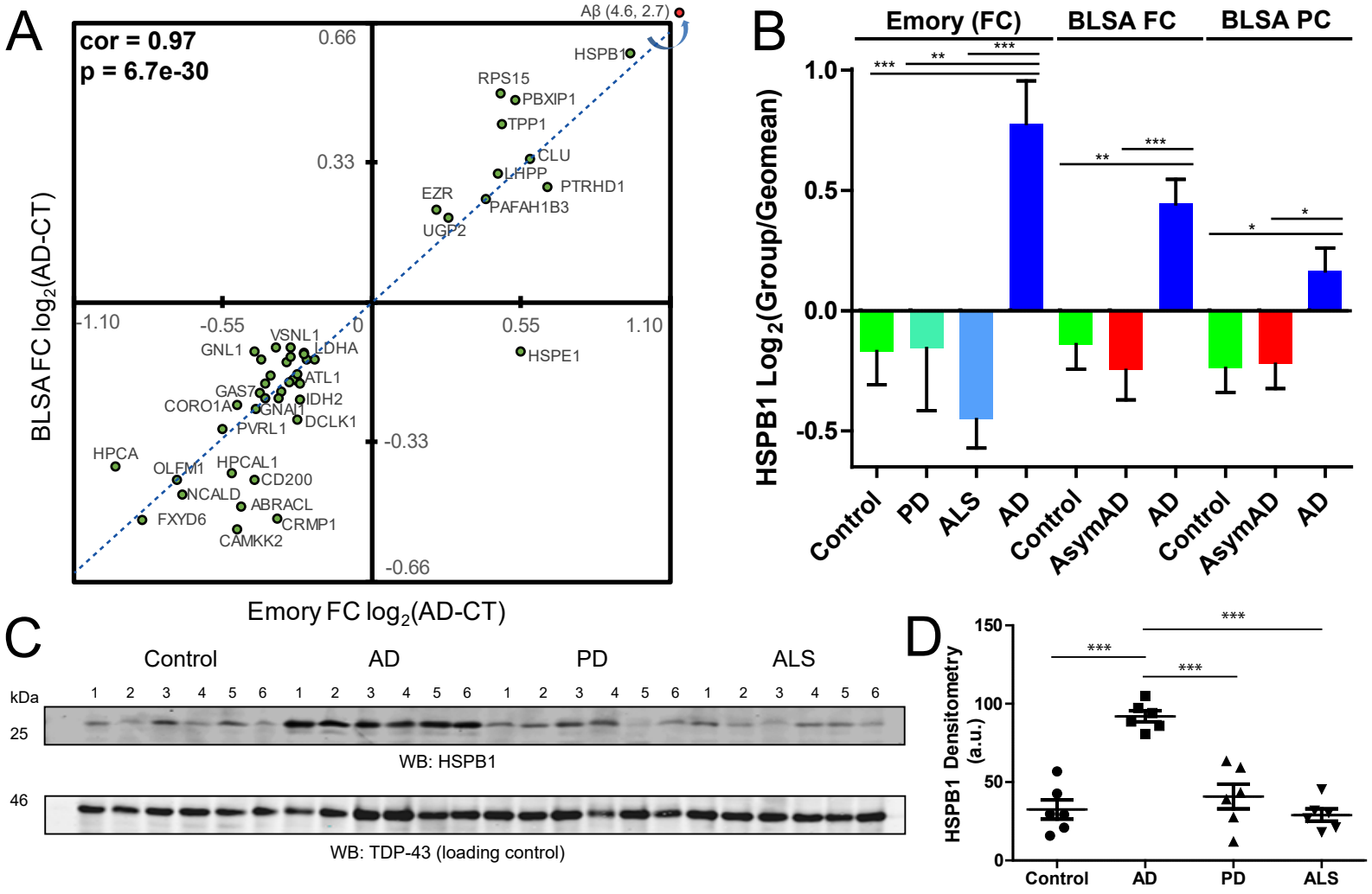
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GNL1
DHA
ATL1
GAS7
IDH2
CORO1A
GNAI1
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NCALD
ABRACL
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CRMP1
CAMKK2
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-0.55
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0.55
1.10
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Emory FC log2(AD-CT)
B
Emory (FC)
BLSA FC
BLSA PC
HSPB1 Log2(Group/Geomean)
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0.5
0.0
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PD
ALS
AD
Control
AsymAD
AD
Control
AsymAD
AD
C
Control
AD
PD
ALS
kDa
25
WB: HSPB1
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PD
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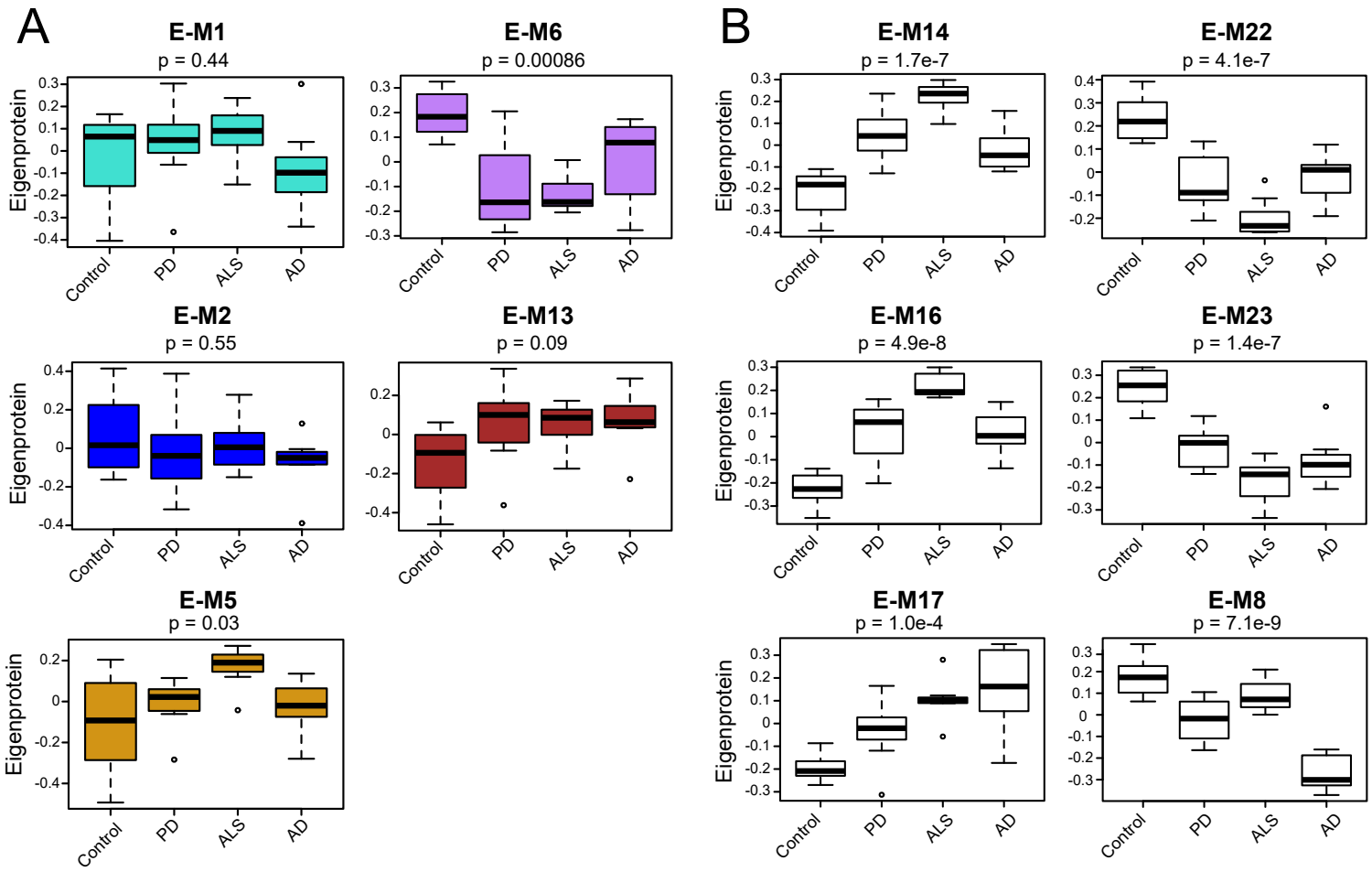
Supplemental Figure 5



Supplemental Figure 6