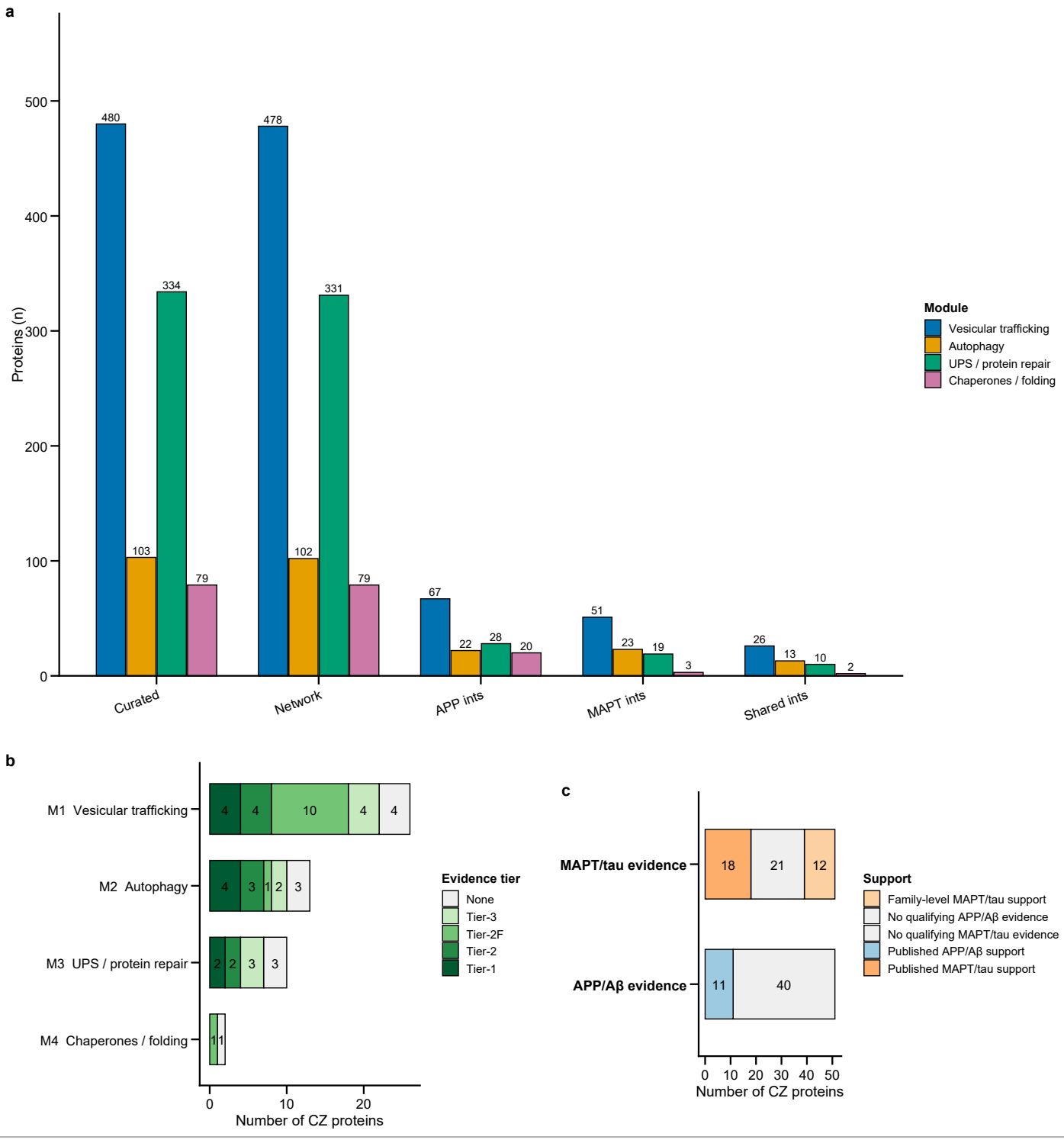
Supplementary Figure 1

Supplementary Figure 1 | STRING protein-protein interaction networks for all four proteostasis modules.

a-d High-confidence STRING networks (combined score >= 0.700) for M1 (Vesicular trafficking), M2 (Autophagy), M3 (UPS / protein repair), and M4 (Chaperones / folding), respectively. Node size is proportional to IVI percentile within the module. Gold border = convergence-zone (CZ) protein (labelled). Layout: Fruchterman-Reingold (fixed random seed).

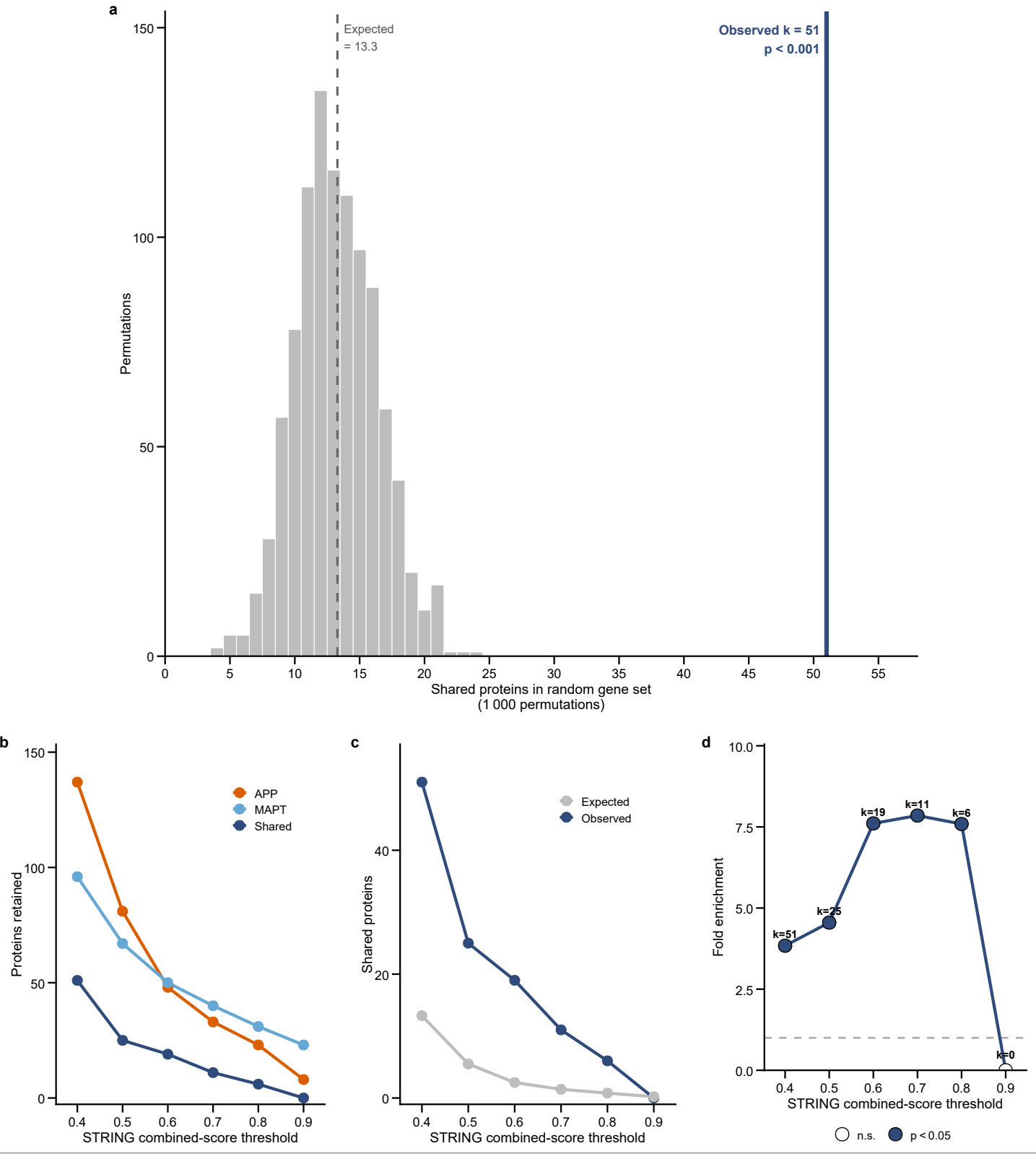
Supplementary Figure 2



Supplementary Figure 2 | Framework construction metrics and CZ protein evidence summary.

a Curated proteins, network proteins, APP interactors, MAPT interactors, and shared interactors per module (dodged bar; counts labelled). **b** Evidence tier of CZ proteins per module (stacked bar; Tier-1 = highest-confidence direct interaction evidence). **c** Number of CZ proteins with published APP/Abeta or MAPT/tau experimental support (stacked bar).

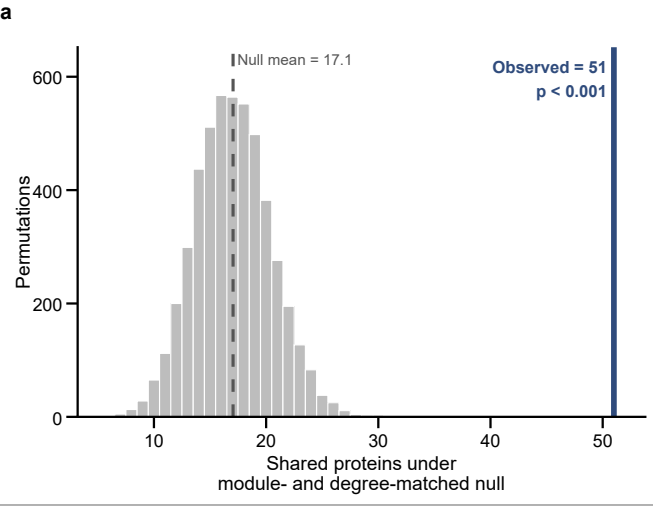
Supplementary Figure 3

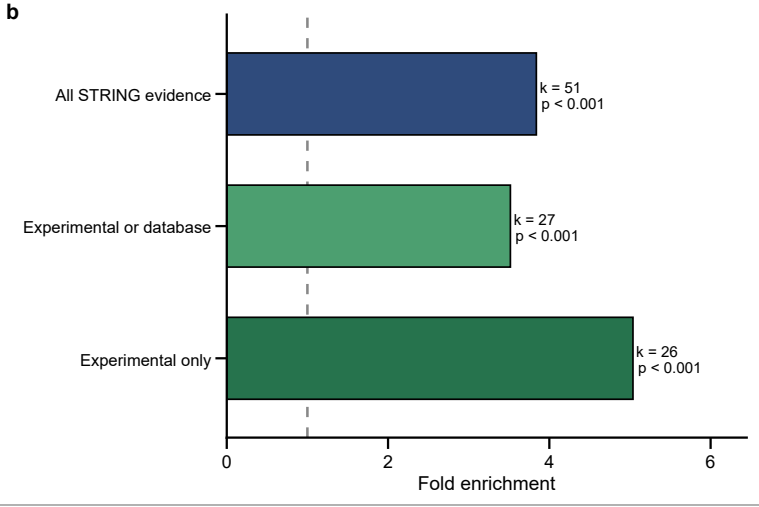


Supplementary Figure 3 | Negative-control random-geneset baseline and STRING threshold sensitivity.

a Permutation histogram of shared-protein counts from 1,000 random gene sets matched in size to the APP and MAPT interactomes; solid line = observed overlap (k); dashed line = hypergeometric expectation. **b** APP interactor count, MAPT interactor count, and shared protein count across STRING combined-score thresholds 0.40-0.90. **c** Observed vs expected shared proteins across thresholds. **d** Fold enrichment across thresholds; filled points indicate p < 0.05; label = observed k.

Supplementary Figure 4

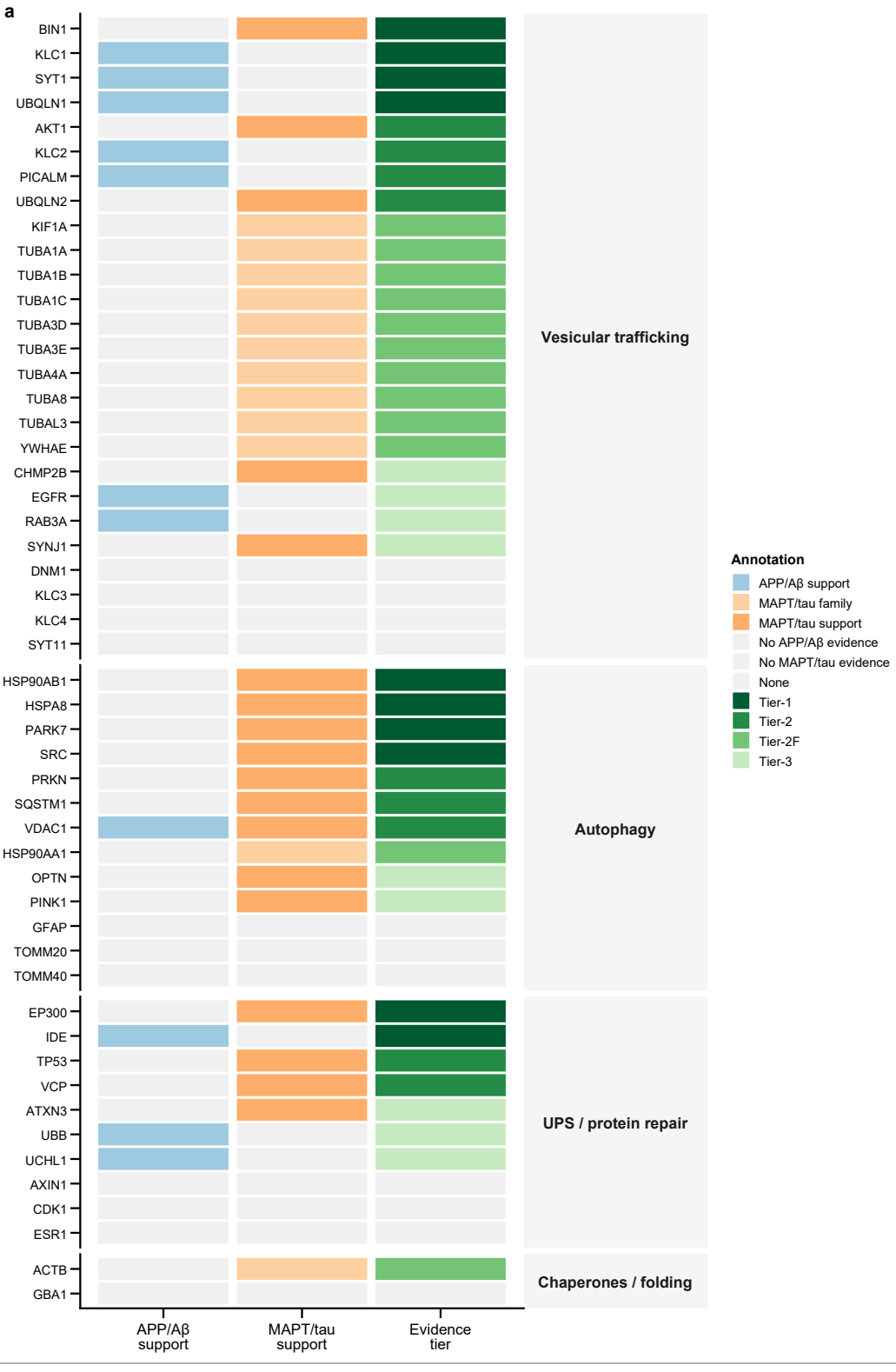




Supplementary Figure 4 | Degree-matched permutation null and evidence-restricted fold-enrichment controls.

a Degree-matched permutation null: observed convergence-zone overlap versus a null distribution generated from module- and degree-stratified random APP and MAPT set pairs matched to the observed per-module counts and within-module degree quintiles (5,000 permutations); solid line = observed value. **b** Fold enrichment of CZ protein co-membership restricted to interactome subsets stratified by interaction evidence type.

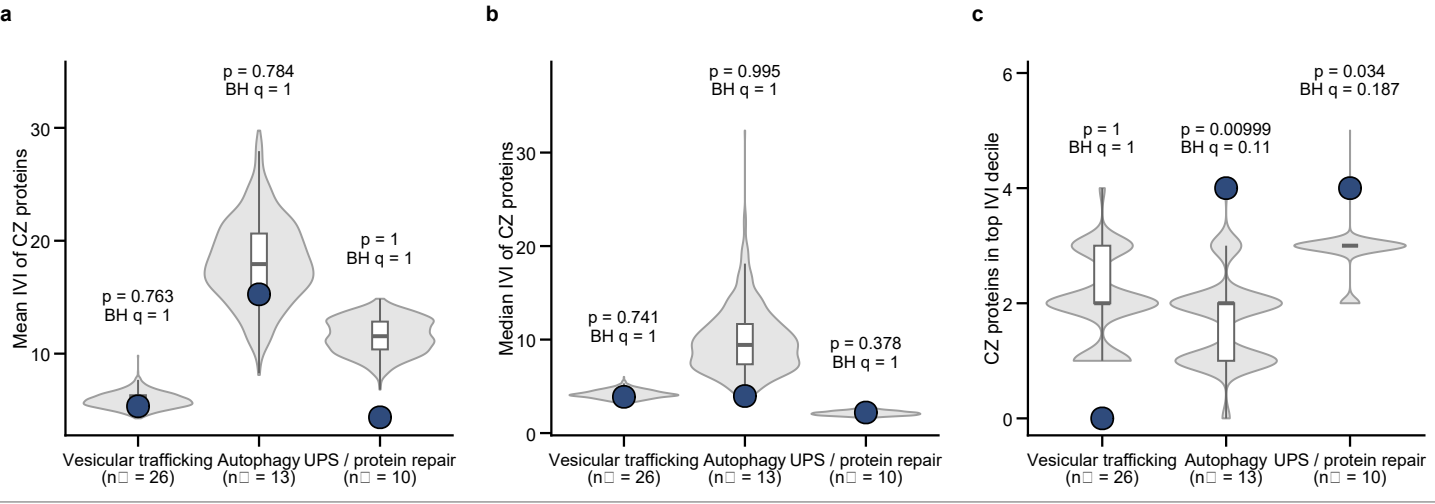
Supplementary Figure 5



Supplementary Figure 5 | Per-protein experimental evidence heatmap for all convergence-zone proteins.

a Heatmap showing APP/Abeta support, MAPT/tau support, and evidence tier (Tier-1 to No evidence retrieved) for each CZ protein, grouped by module. Tier-1: direct physical interaction with APP or MAPT; Tier-2: biochemical or genetic co-occurrence; Tier-2 (family): family-level evidence; Tier-3: indirect or computational.

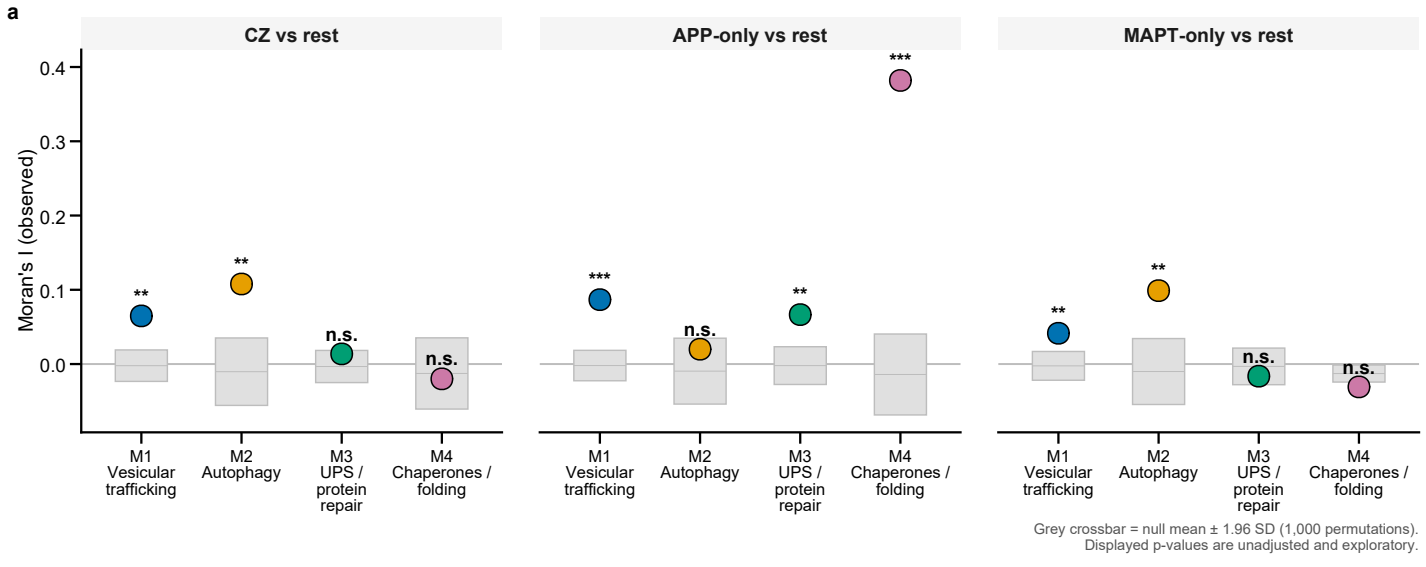
Supplementary Figure 6



Supplementary Figure 6 | Degree-preserving IVI topology null distributions for modules M1-M3.

a Mean IVI of CZ proteins (observed, filled point) versus degree-preserving permutation draws (violin + box); empirical p shown above. **b** Median IVI of CZ proteins versus null. **c** Count of CZ proteins in the top IVI decile versus null. M4 was excluded from formal module-level inference because it contained only two CZ proteins (ACTB and GBA1); its topology results are descriptive.

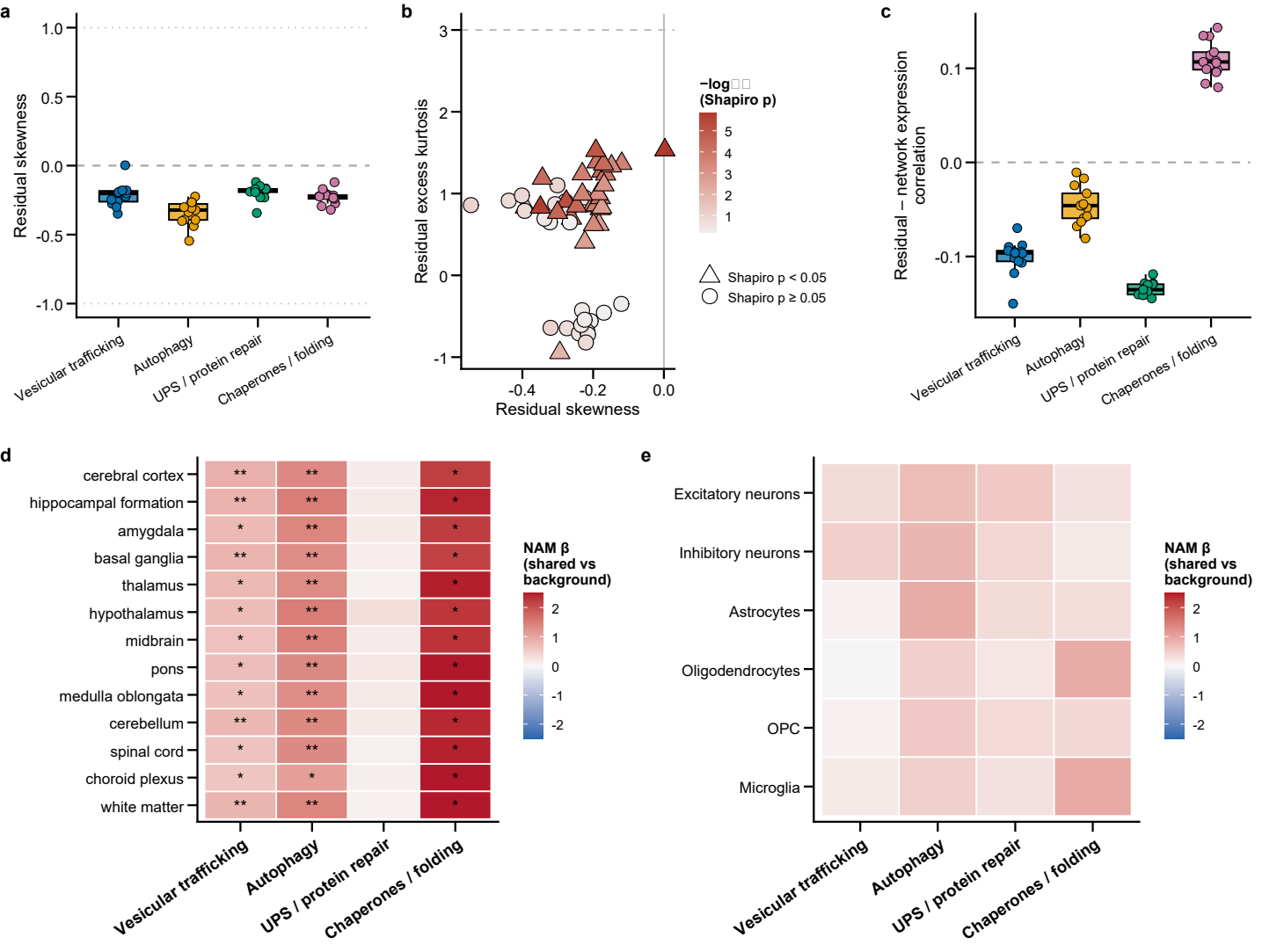
Supplementary Figure 7



Supplementary Figure 7 | Binary Moran's I spatial-autocorrelation tests for all group-membership contrasts.

a Observed Moran's I (filled circle) for three contrasts - CZ vs rest, APP-only vs rest, MAPT-only vs rest - across all four modules. Grey crossbar = null mean +/- 1.96 SD (1,000 permutations). Stars: *** p < 0.001, ** p < 0.01, * p < 0.05.

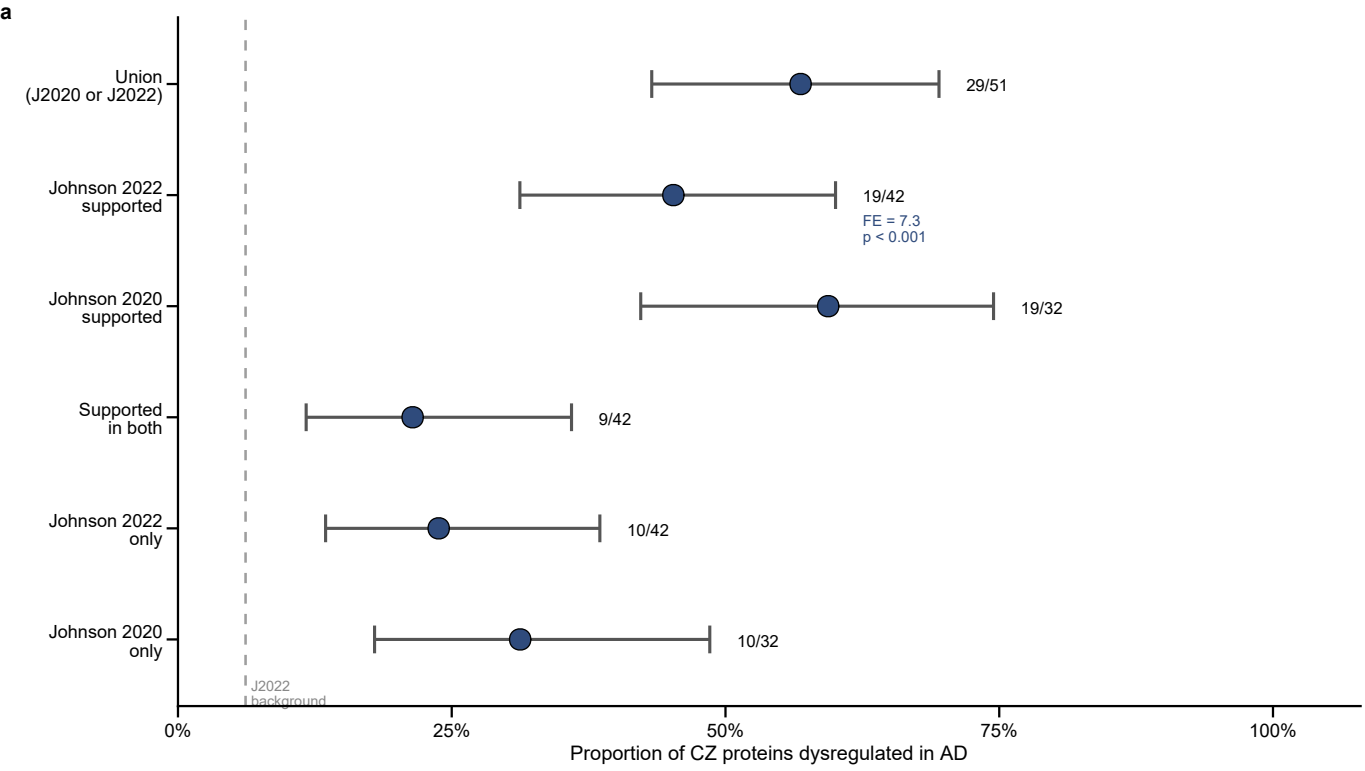
Supplementary Figure 8

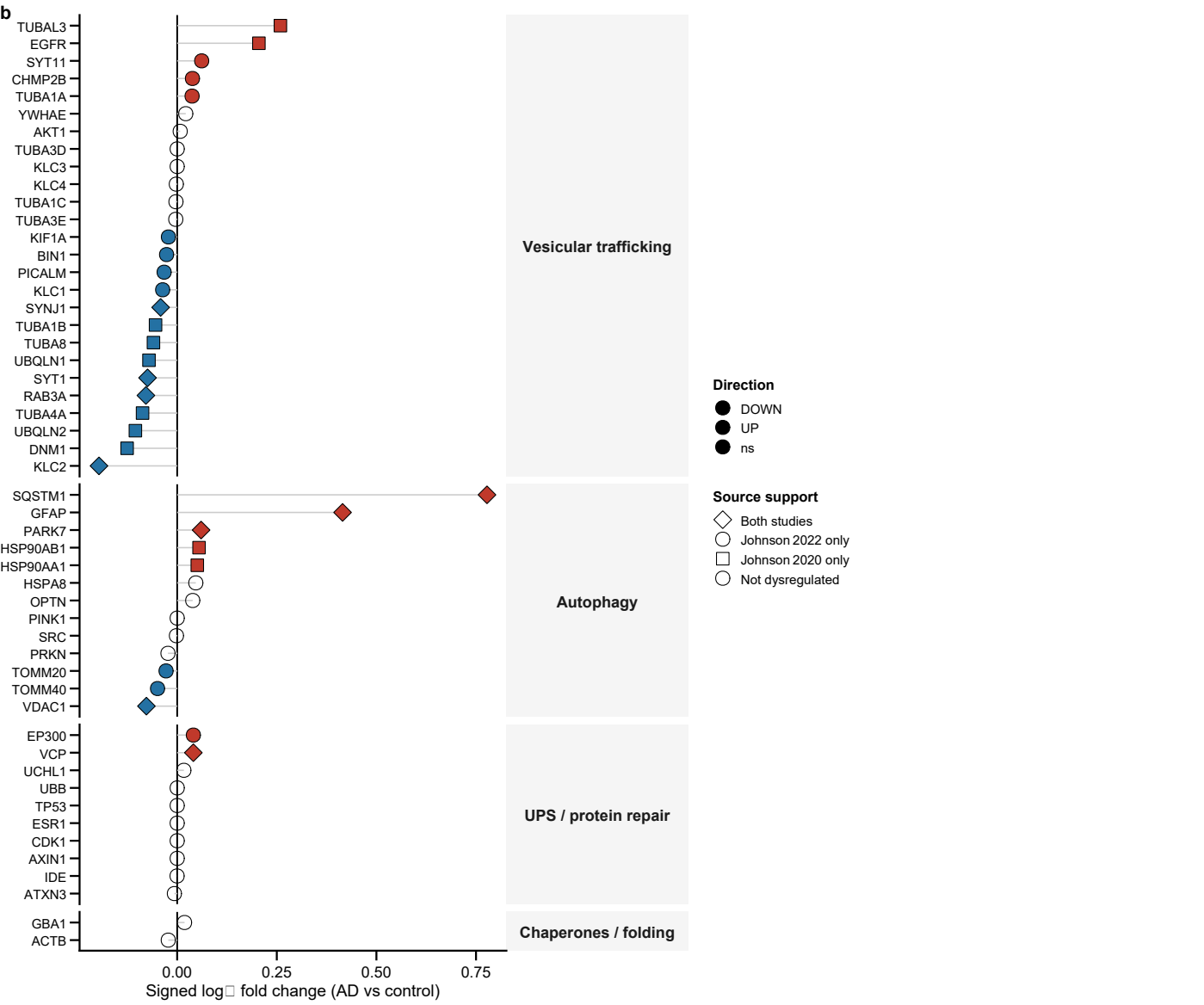


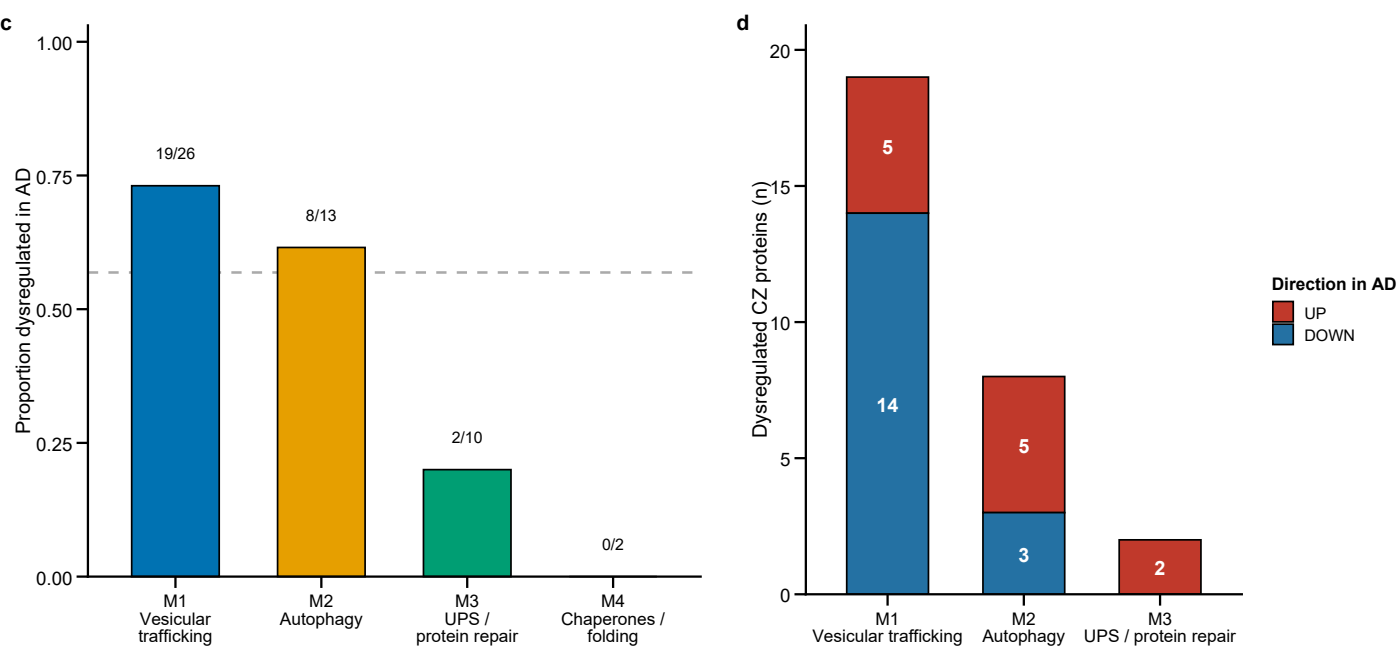
Supplementary Figure 8 | Network-adjusted model (NAM) residual diagnostics and full expression heatmaps.

a Residual skewness per module (box + jitter; dashed = 0; dotted = +/-1). **b** Residual skewness vs excess kurtosis scatter; colour = -log10(Shapiro-Wilk p); triangle = Shapiro p < 0.05. **c** Residual-network expression correlation per module (box + jitter; dashed = 0). **d** NAM beta coefficient heatmap across 13 brain regions x 4 modules (blue-red diverging scale; **, * = FDR-corrected; dagger = nominal p < 0.05). **e** NAM beta heatmap across 6 major cell types x 4 modules.

Supplementary Figure 9



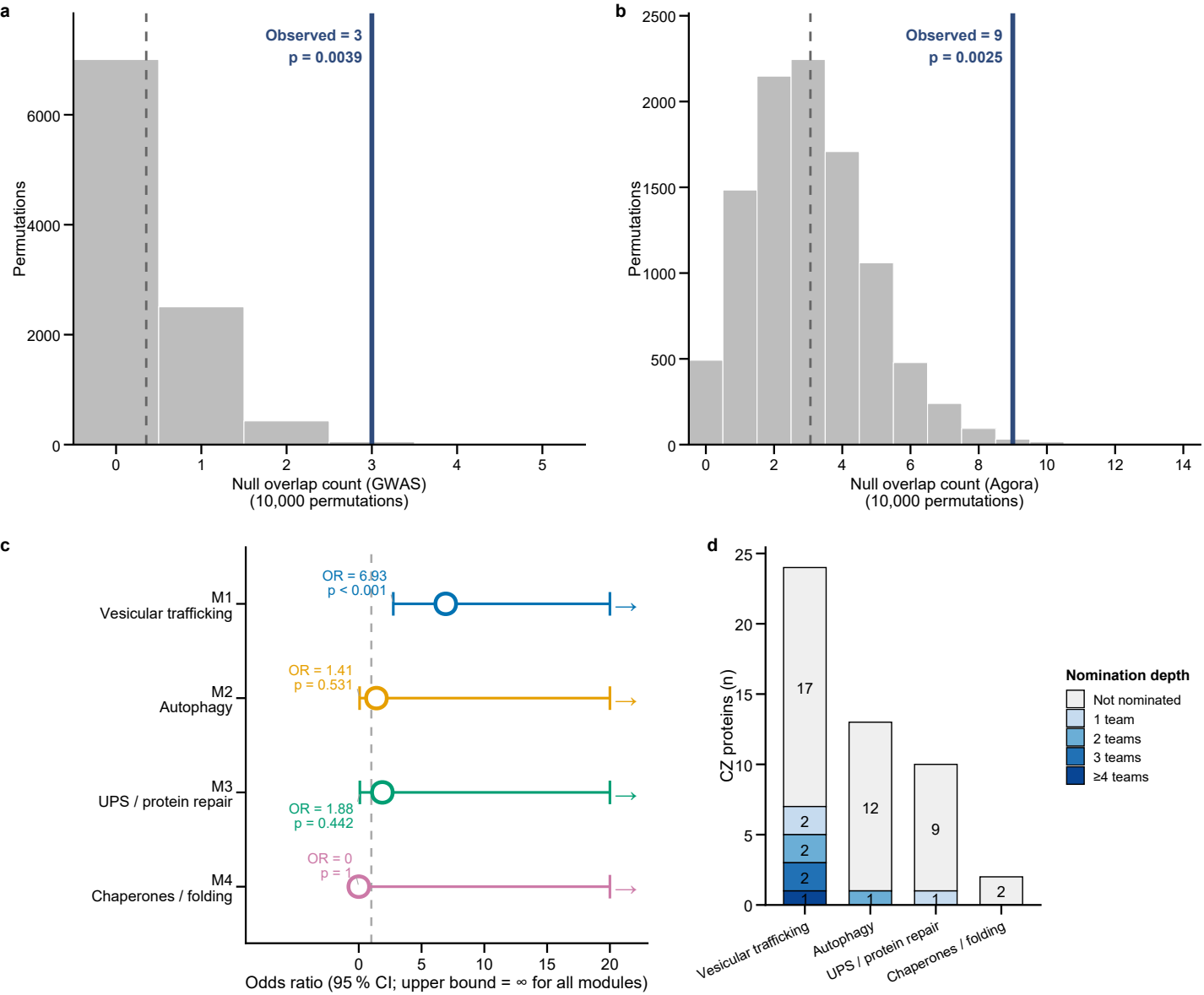




Supplementary Figure 9 | AMP-AD proteomics validation - source sensitivity, per-gene fold change, and module dysregulation.

a Source-aware proportions of CZ proteins with study support, shown with 95% Wilson confidence intervals; labels indicate n supported/n eligible. The Johnson 2022 row is inferential (19/42 measured, rate 45.2%, fold enrichment 7.33, hypergeometric P = 8.99 × 10^-13); all other rows (Johnson 2020, union and subset rows) are descriptive only because no valid corresponding background rate was available. **b** Per-protein signed log2 fold change (AD vs control) for all 51 CZ proteins, faceted by module; shape = source study, fill = direction; PRKN measured (J2022) but not significantly dysregulated. **c** Module-wise union dysregulation rates with 95% Wilson CIs (union = J2020 or J2022 significant; all modules exploratory/descriptive): M1 19/26, M2 8/13, M3 2/10, M4 0/2. **d** Directional breakdown (up / down stacked bar) per module.

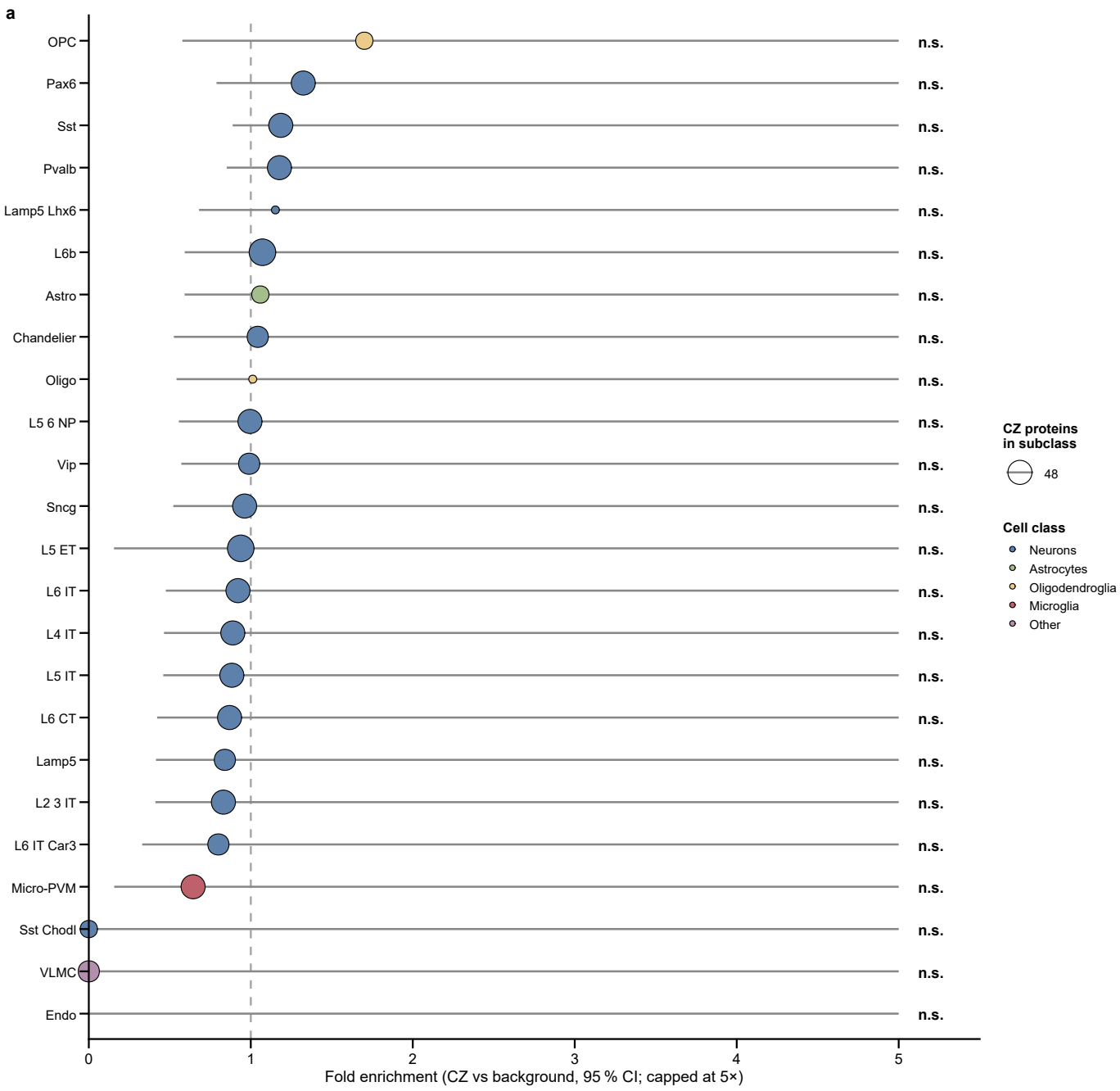
Supplementary Figure 10



Supplementary Figure 10 | GWAS and Agora validation - permutation nulls and per-module enrichment.

a GWAS permutation null histogram (10,000 permutations); solid line = observed overlap; empirical p labelled. **b** Agora permutation null histogram (same approach). **c** Per-module Agora Fisher exact test odds ratio (95% CI; upper bounds extend to infinity for all modules, indicated by right-arrow); dashed line = OR 1. **d** Agora nomination-depth stacked bar: CZ proteins nominated by 0 to >=4 Agora scoring teams per module.

Supplementary Figure 11



Supplementary Figure 11 | SEA-AD single-nucleus transcriptomics - CZ protein DEG enrichment by cell-type subclass.

a Fold enrichment of CZ protein differentially expressed genes relative to background for each MTG cell-type subclass, ranked in descending order. Point size = number of CZ proteins in subclass; colour = broad cell class (Neurons, Astrocytes, Oligodendroglia, Microglia). CI bars capped at 5x. Dashed line = fold enrichment 1. No subclass reached nominal significance ($p < 0.05$).