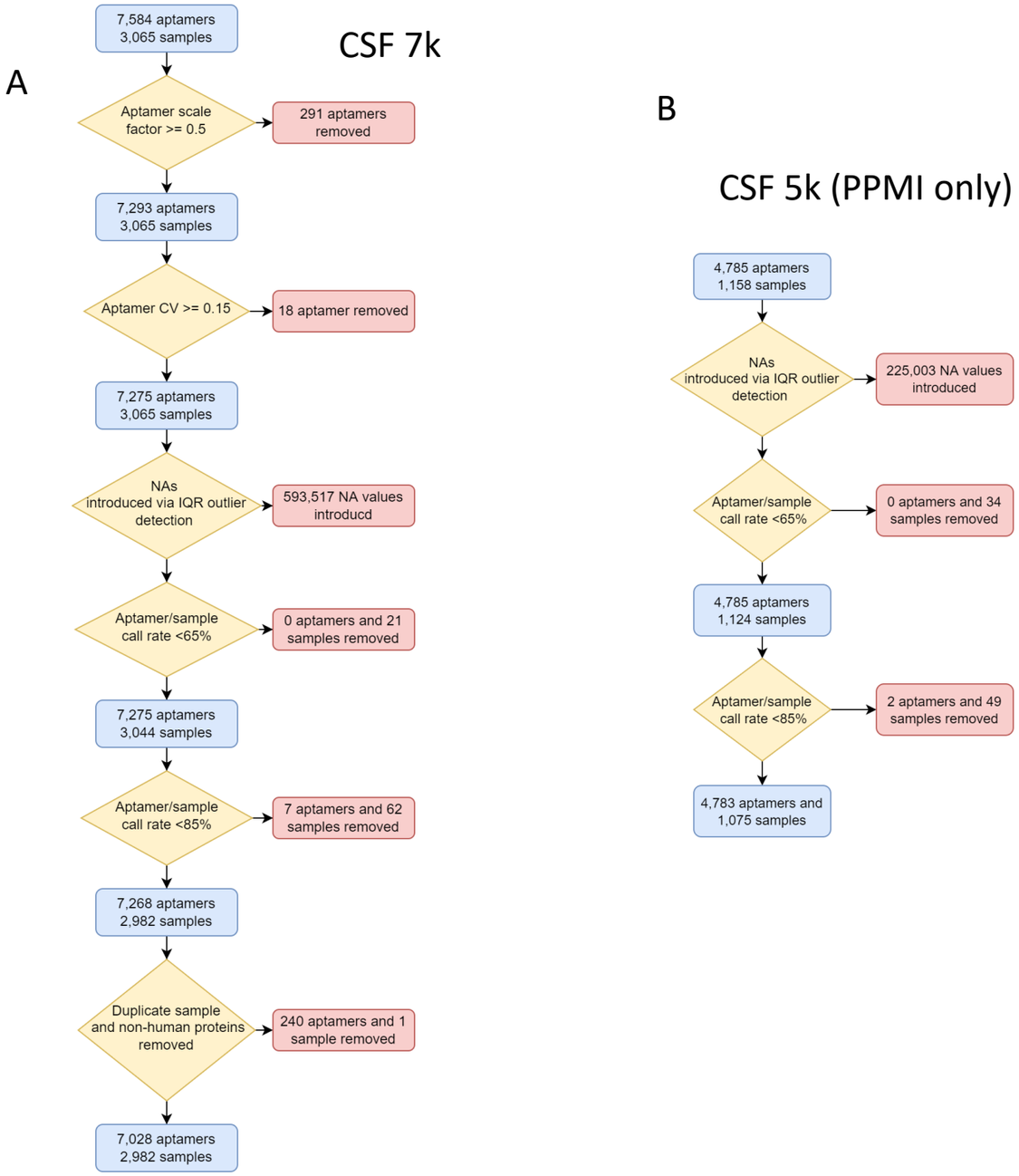
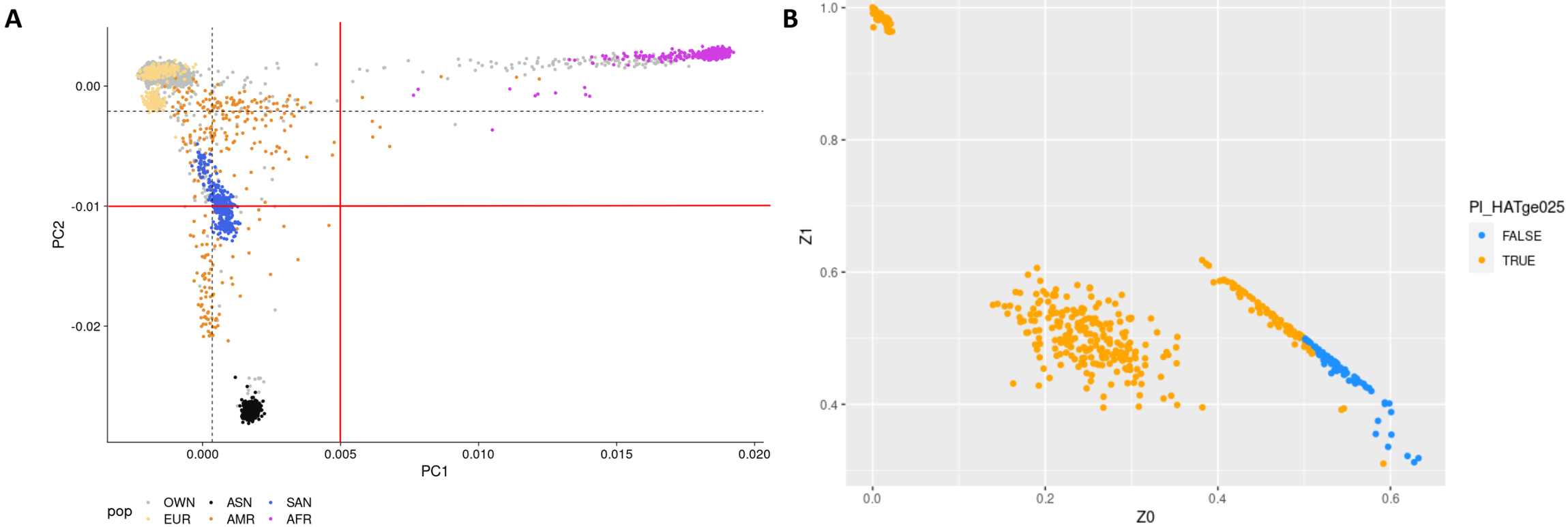
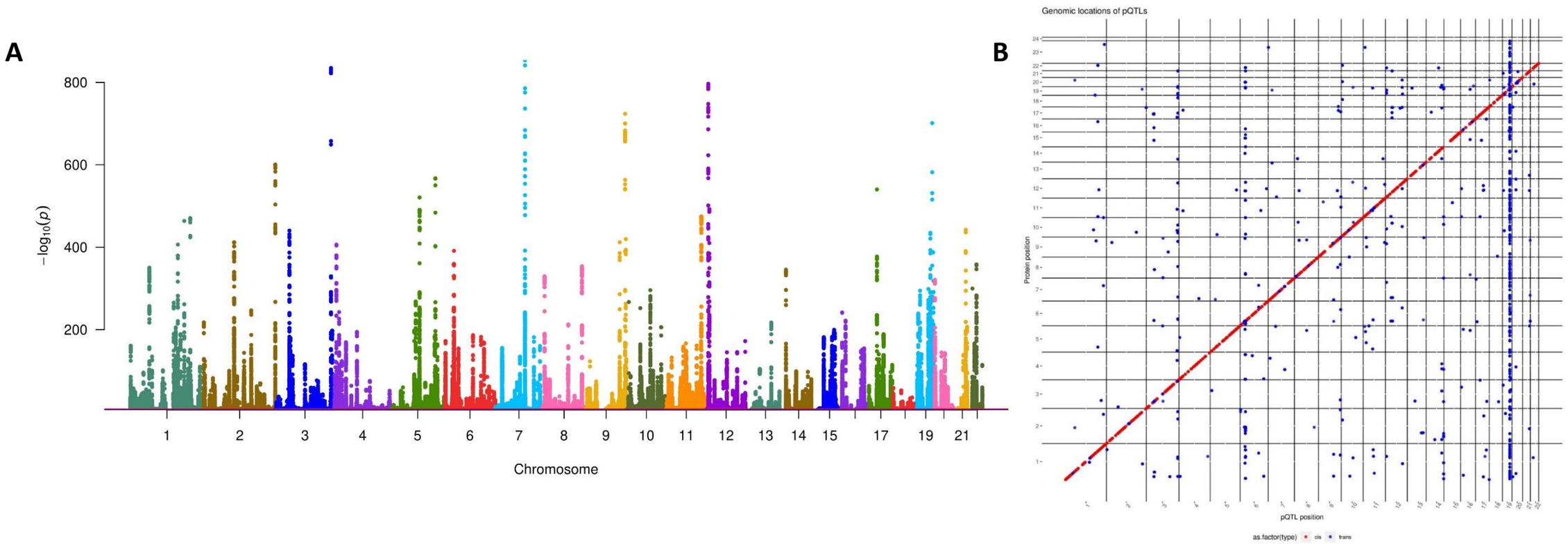


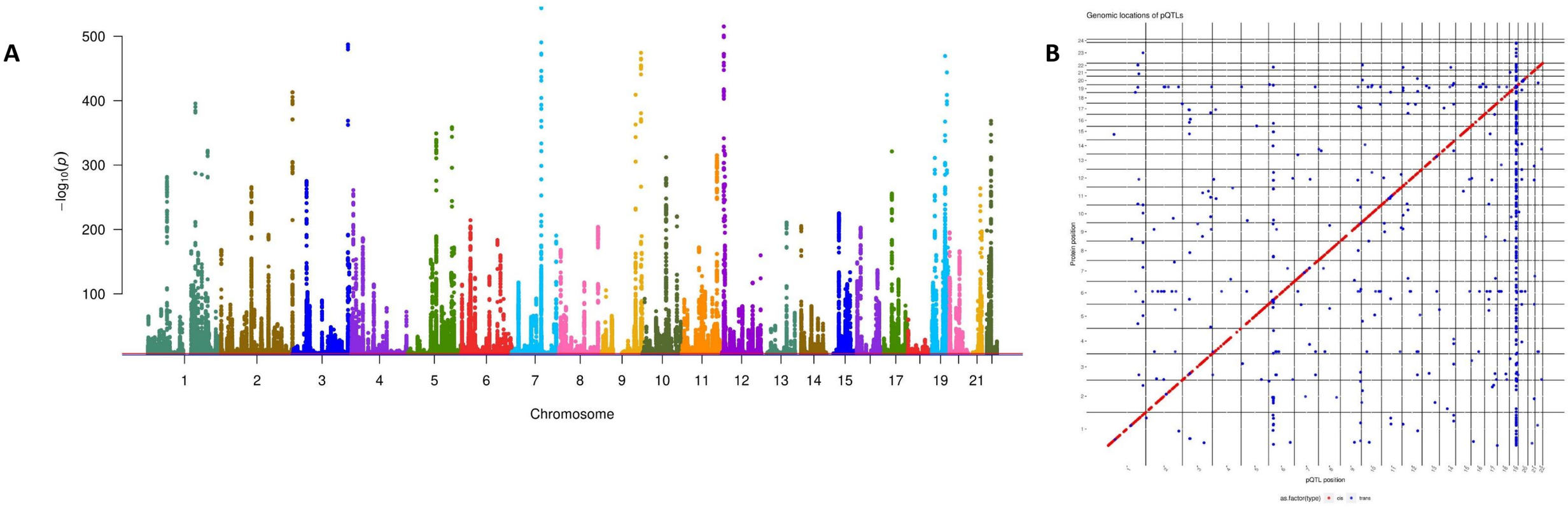
Supplementary Figure 1: Proteomics QC. A. Quality control steps for all samples and aptamers measured using the SOMAscan7k platform. **B.** Quality control steps for all samples and aptamers measured using the SOMAscan5k platform. CV: coefficient of variation; IQR: interquartile range.



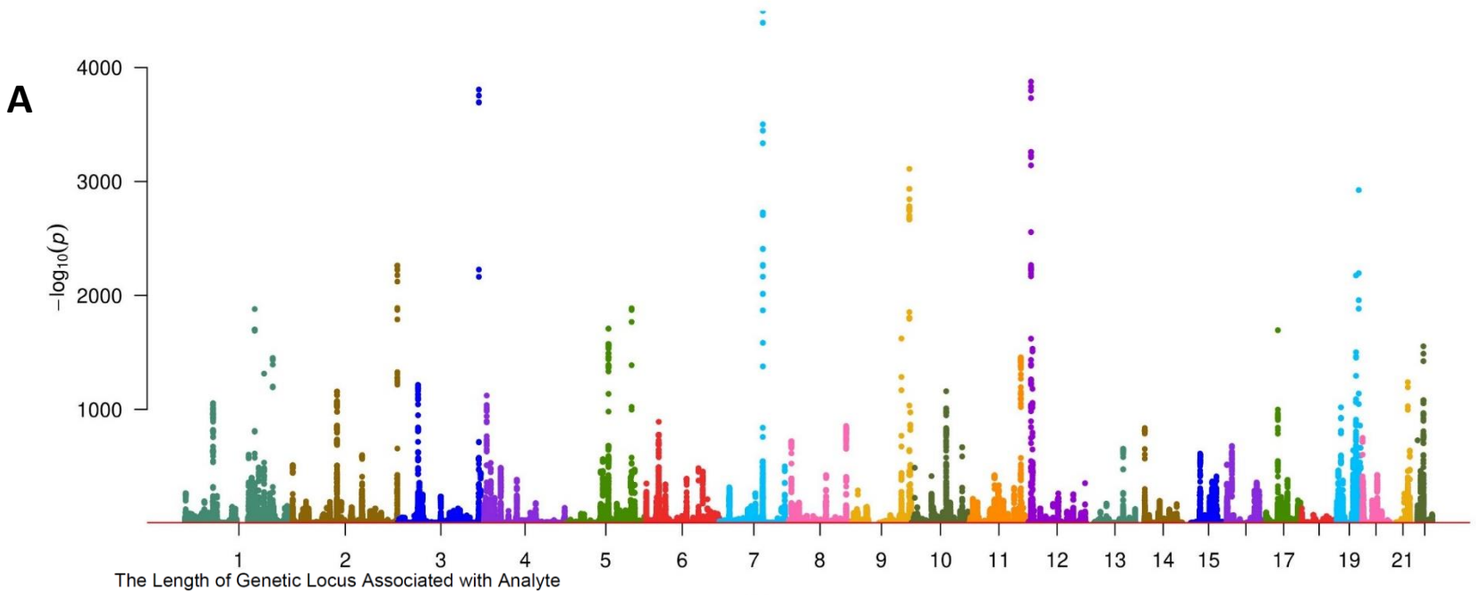
Supplementary Figure 2: GWAS Data QC. A. Scatter plot of the first two genetic principal components for our samples. We first used broad filtering (red lines, PC1 < 0.005, PC2 > -0.01) then from the remaining samples calculated the standard deviation (SD) and kept all samples within 3 SD of the mean (dashed lines), corresponding to non-Hispanic white samples. **B.** Scatter plot of relatedness as determined by IBD. Orange dots correspond to pairs with PI_HAT ≥ 0.25; one from each of these pairs was removed.

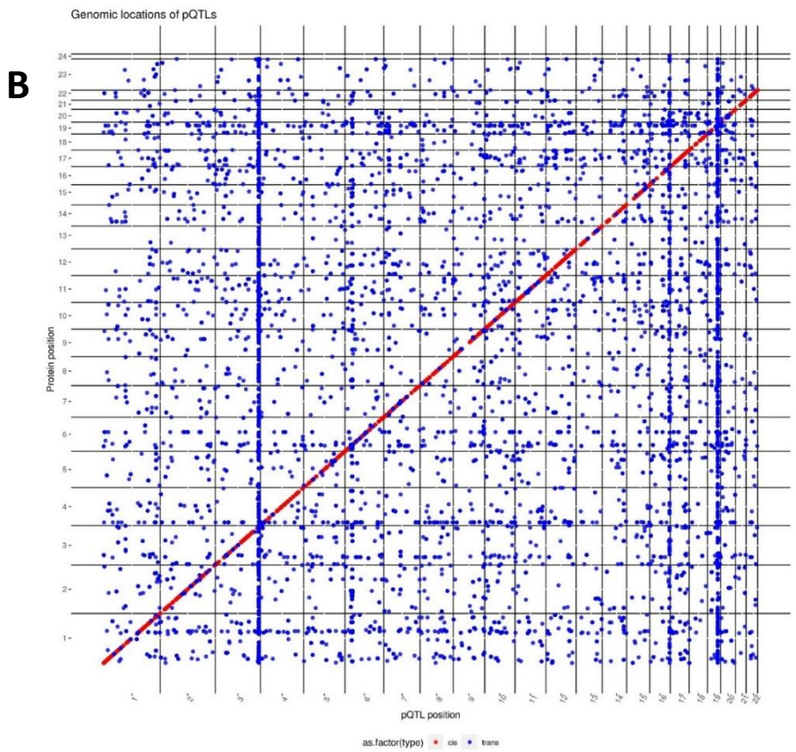


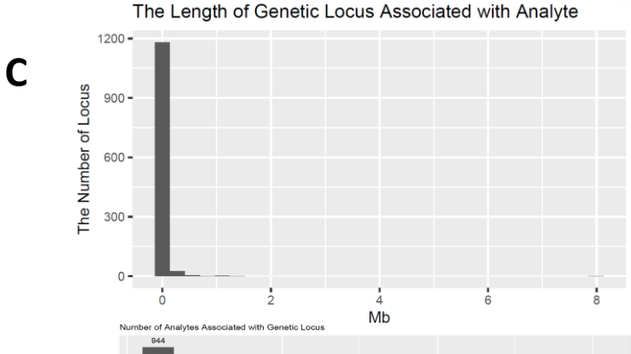
Supplementary Figure 3: Discovery-specific analyses. A. Combined Manhattan plot showing the pQTL results from the discovery analysis of 1,912 individuals and 7,559 aptamers. X-axis: genomic position of each variant; y-axis: -log10(P-value) of association between a variant and aptamer level. **B.** 2D Manhattan plot showing the pQTL results from the discovery analysis. X-axis: location of the index pQTL variant for each association; y-axis: location of the gene encoding the protein associated with each genetic variant. Colors represent *cis* (red) and *trans* (blue) associations.

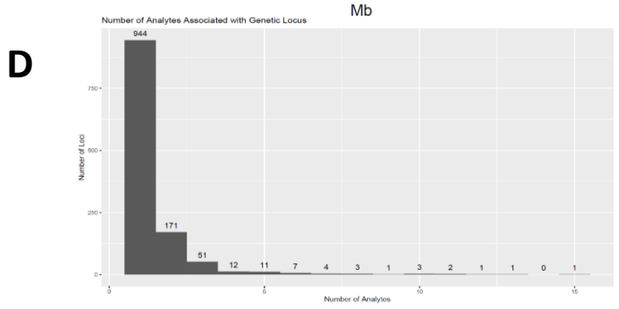


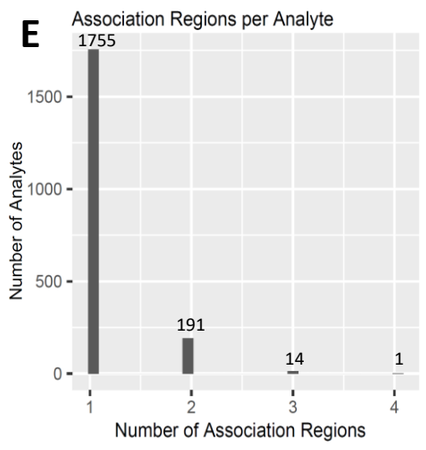
Supplementary Figure 4: Replication-specific analyses. A. Combined Manhattan plot showing the pQTL results from the replication analysis of 1,195 individuals and 7,028 aptamers. X-axis: genomic position of each variant; y-axis: -log10(P-value) of association between a variant and aptamer level. **B.** 2D Manhattan plot showing the pQTL results from the replication analysis. X-axis: location of the index pQTL variant for each association; y-axis: location of the gene encoding the protein associated with each genetic variant. Colors represent *cis* (red) and *trans* (blue) associations.

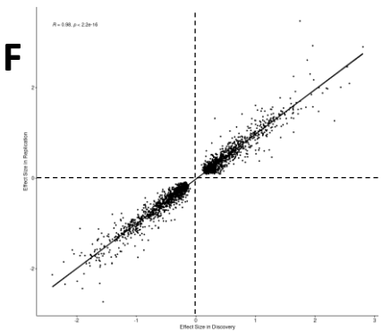


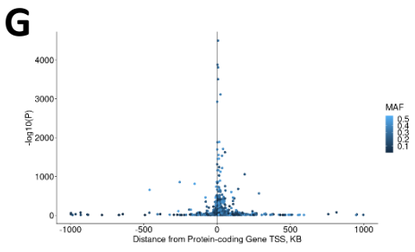


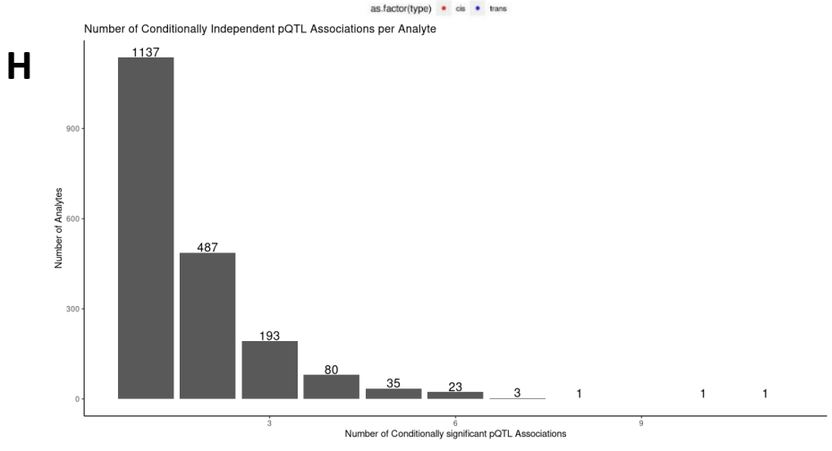




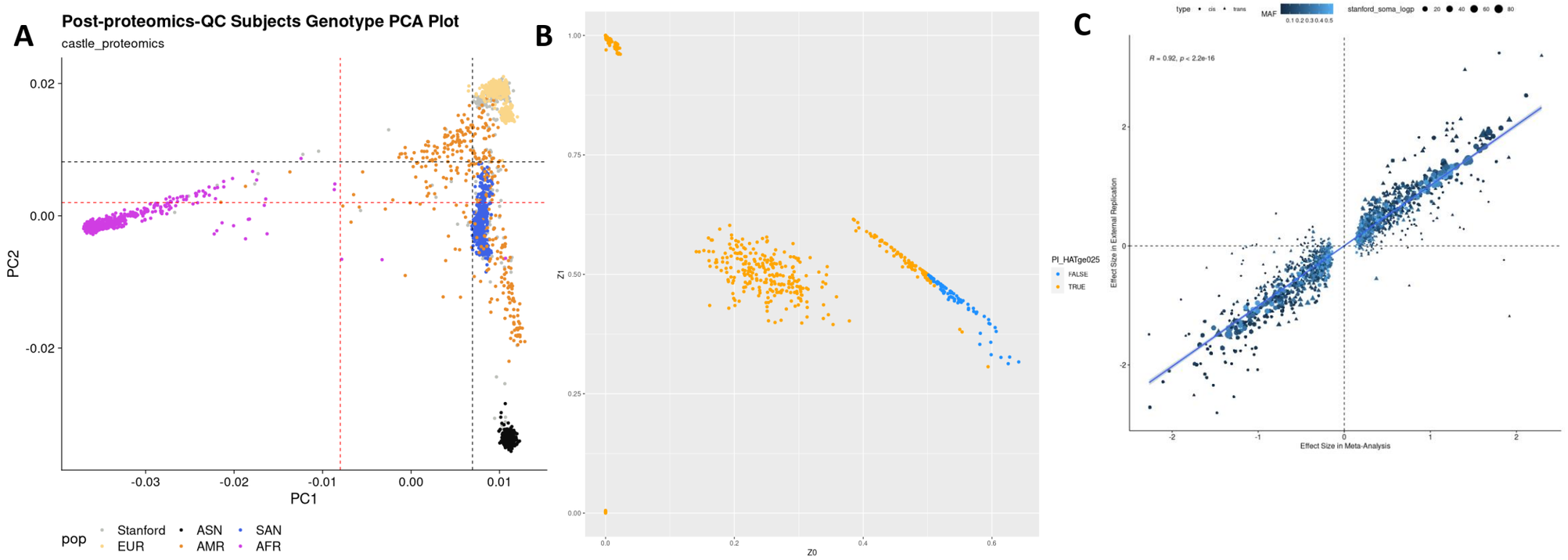




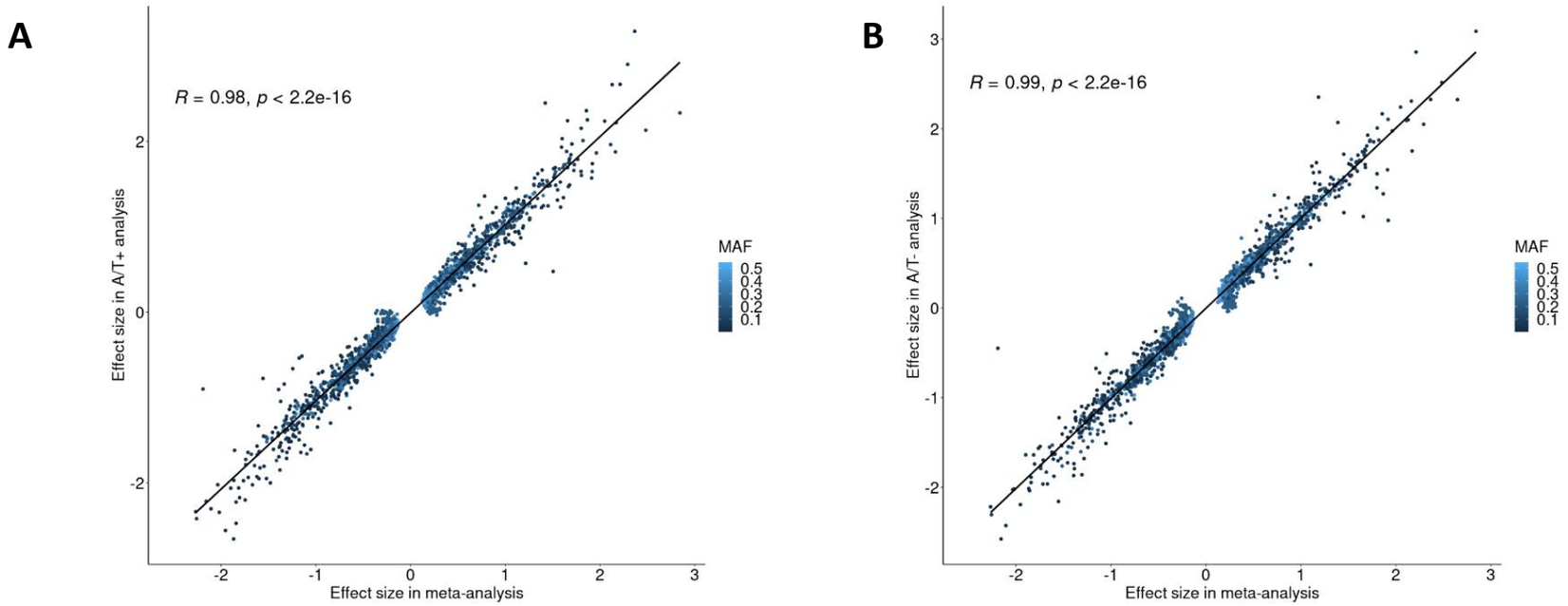




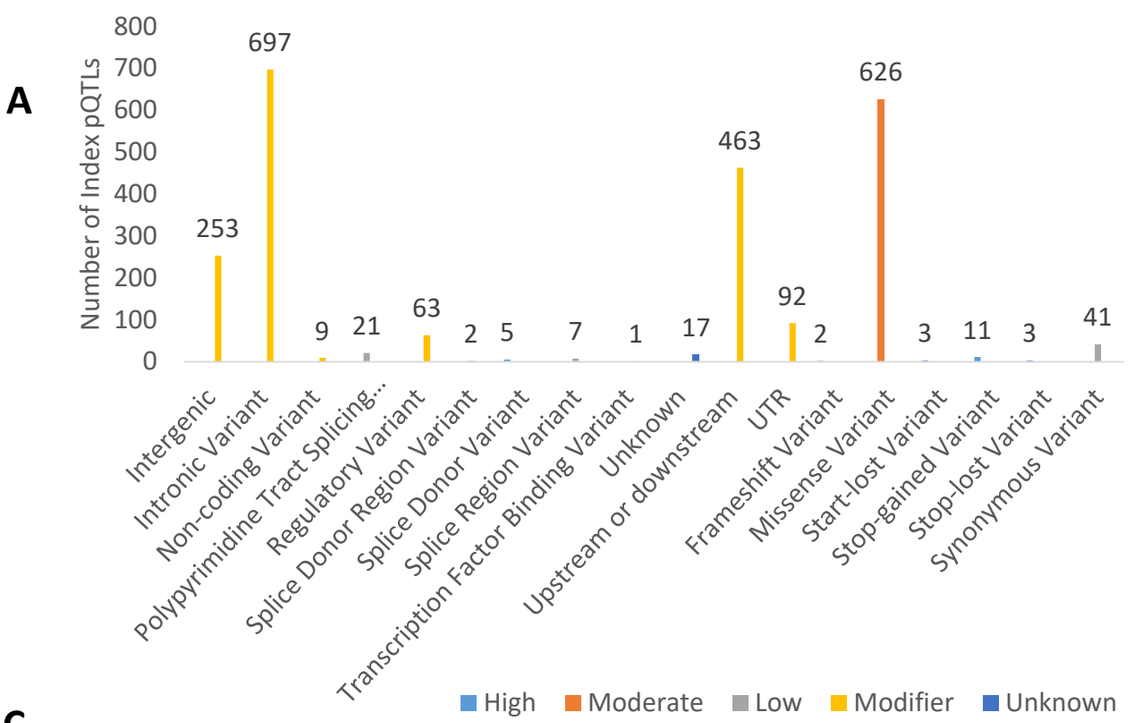
Supplementary Figure 5: Meta-analysis secondary analyses. A. Combined Manhattan plot showing the pQTL results from the meta-analysis of 3,107 total samples and 7,028 aptamers. X-axis: genomic position of genetic variants; y-axis: -log10(P-value) for the association between a genetic variant and the levels of an aptamer. **B.** 2D Manhattan plot showing the all genome-wide significant associations in the meta-analysis ($P < 5\times10^{-8}$). X-axis: genomic position of genetic variants associated with protein levels, split by chromosome; y-axis: genomic position of the gene encoding each protein. Colors represent *cis* associations (red) and *trans* associations (blue). **C.** Histogram showing the length of each pQTL region, representing the distance in megabases between the two variants denoting the end of a region. The regions were determined through LD ($R^2 > 0.1$) between index pQTL variants across all proteins. **D.** Histogram showing the number of aptamers associated with each pQTL region. Three regions with high pleiotropy (number of regulated aptamers = 74, 136, 337) are excluded here but discussed in detail in the main text. **E.** Number of unique index pQTL associations per aptamer. Aptamers with more than one association region have multiple index variants in different genomic regions. **F.** Correlation of 2,316 index pQTL variants in discovery (x-axis; N = 1,912) and replication (y-axis, N = 1,195) analyses. Pearson correlation is reported. Color corresponds to minor allele frequency at the variant (darker = less common). **G.** Scatter plot of *cis* index pQTL variant p-values with distance from the corresponding protein-coding gene. Color corresponds to minor allele frequency (darker = less common). **H.** Histogram of the number of conditionally independent pQTL associations per aptamer (minimum 1) as determined by GCTA-COJO.

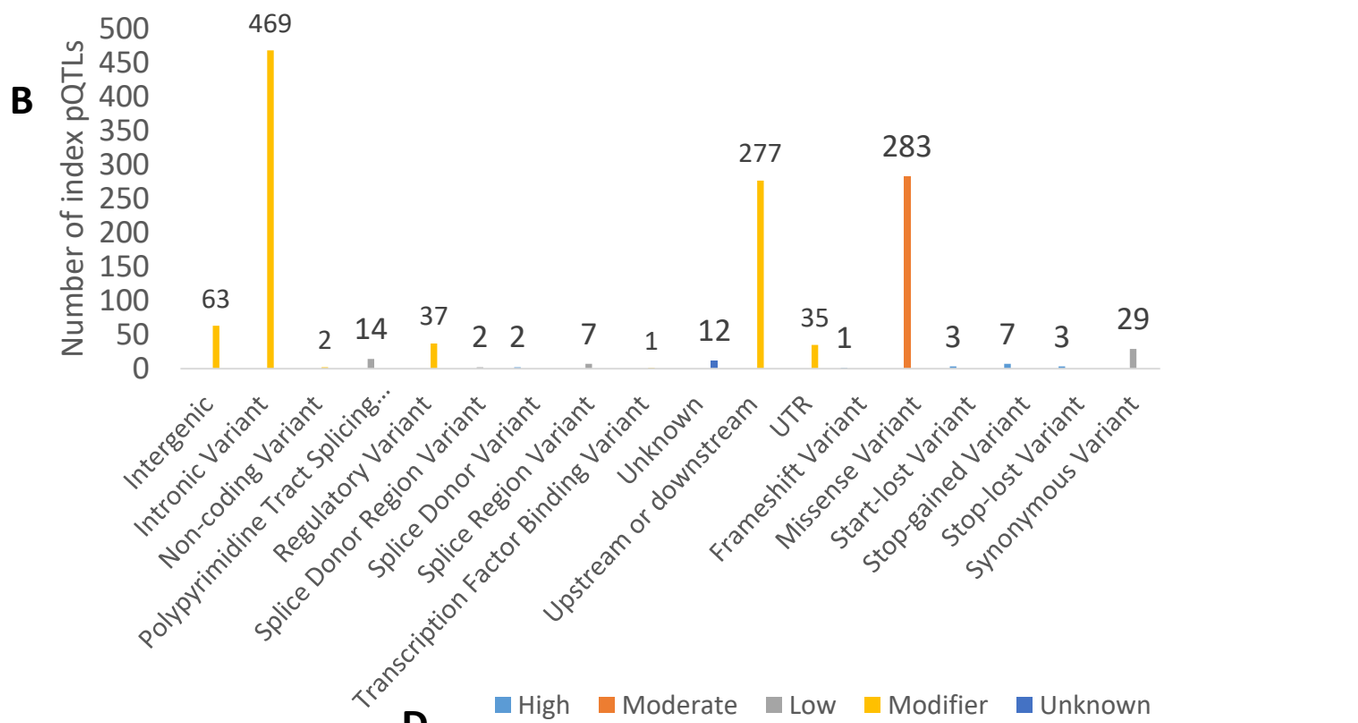


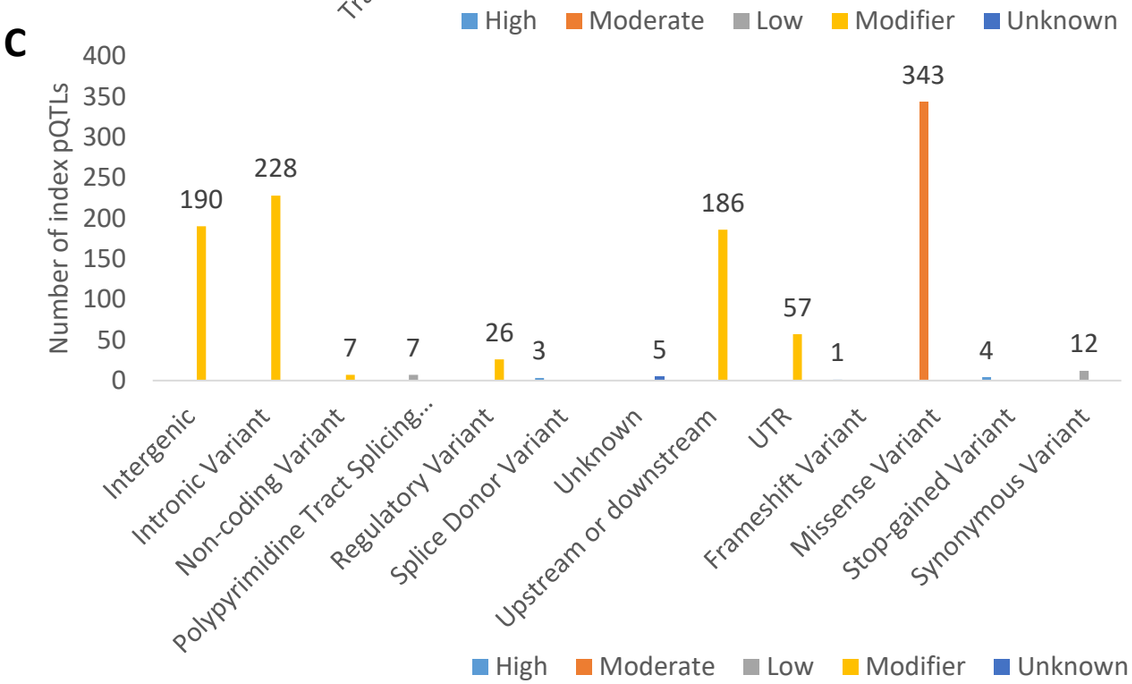
Supplementary Figure 6: Replication in external dataset (Stanford-ADRC, Wagner). A. Scatter plot of the first two genetic principal components for external replication samples using 1000 Genomes as the anchor. We first used broad filtering (dashed red lines, PC1 > -0.008, PC2 > 0.002) then from the remaining samples calculated the standard deviation (SD) and kept all samples within 3 SD of the mean (dashed black lines), corresponding to non-Hispanic white samples. **B.** Scatter plot of relatedness of samples between the 3,107 samples used for discovery & replication and external replication. For all pairs containing a sample from the external replication, that sample was preferentially removed. After PCA & IBD filtering, 460 genomic samples were kept. **C.** Correlation of effect sizes of index pQTL variants between the meta-analysis (x-axis, N = 3,107) and external replication (y-axis, N = 183). Pearson correlation was calculated. Index variants (individual points) are colored by their MAF as obtained from the 3,107 samples. Shape corresponds to *cis* or *trans* variant status (*cis*, circle; *trans,* triangle). Point size corresponds to the –log10(P) for the variant-protein association in the external dataset.

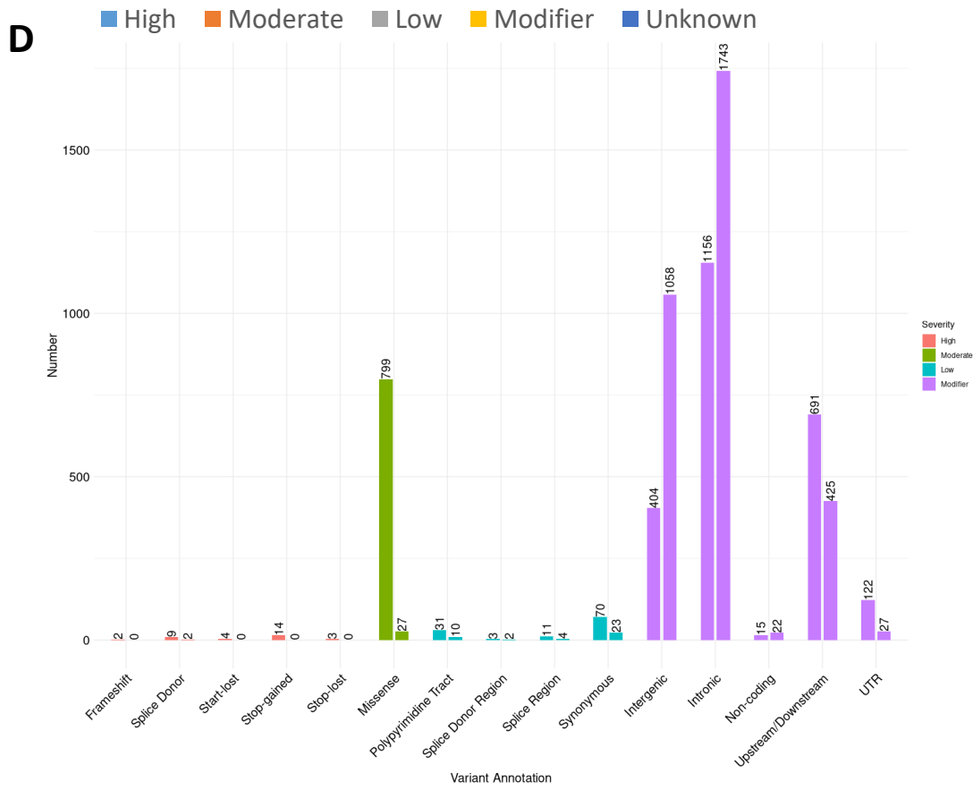


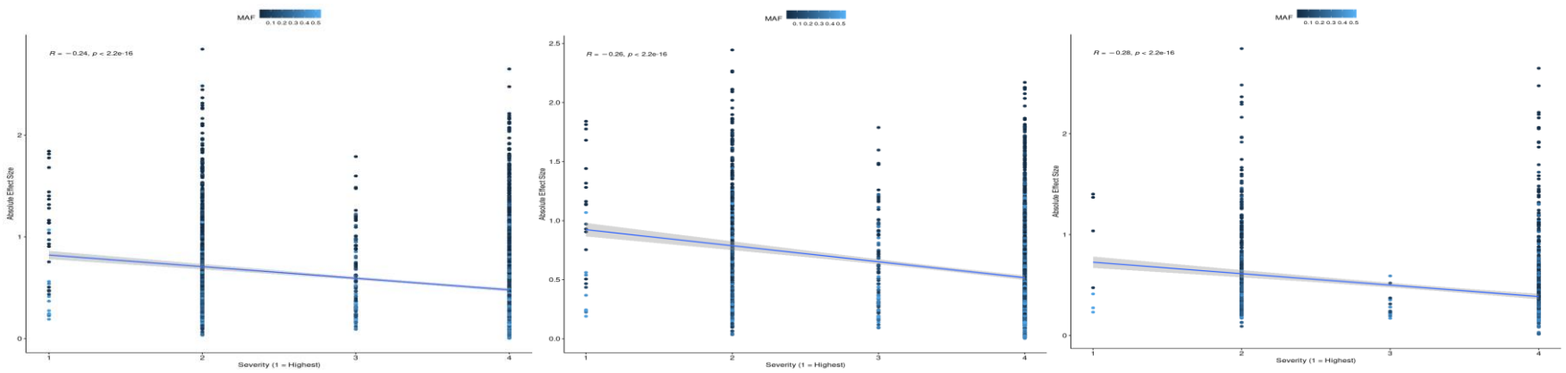
Supplementary Figure 7: Disease-specific analyses. A. Correlation of effect sizes for meta-analysis index pQTL variants in meta-analysis (x-axis, N = 3,107) and in CSF amyloid/tau positive individuals (y-axis, N = 775). Color represents minor allele frequency (darker = less common). **B.** Correlation of effect sizes for meta-analysis index pQTL variants in meta-analysis (x-axis, N = 3,107) and in CSF amyloid/tau negative individuals (y-axis, N = 889). Color represents minor allele frequency (darker = less common).



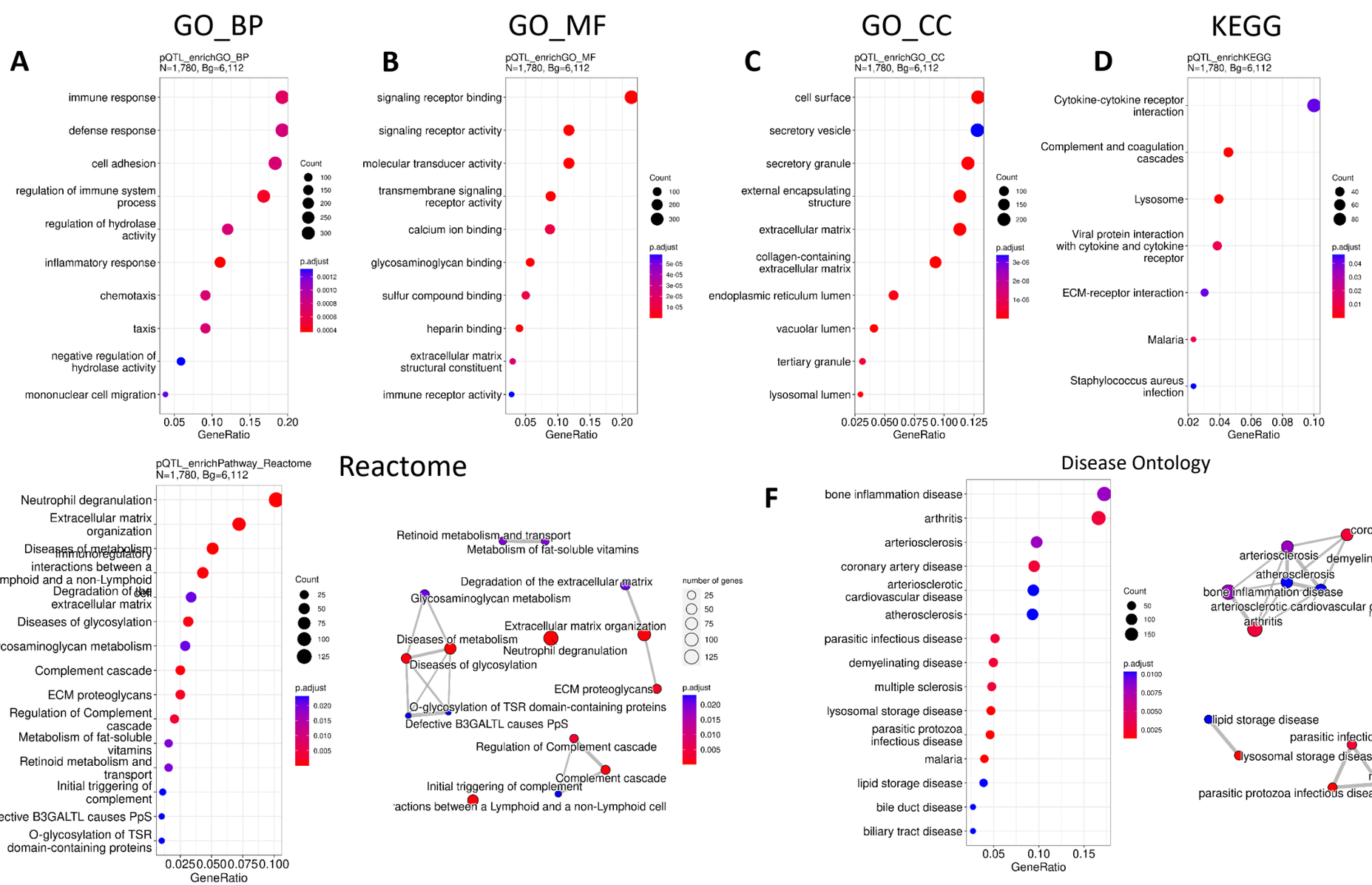




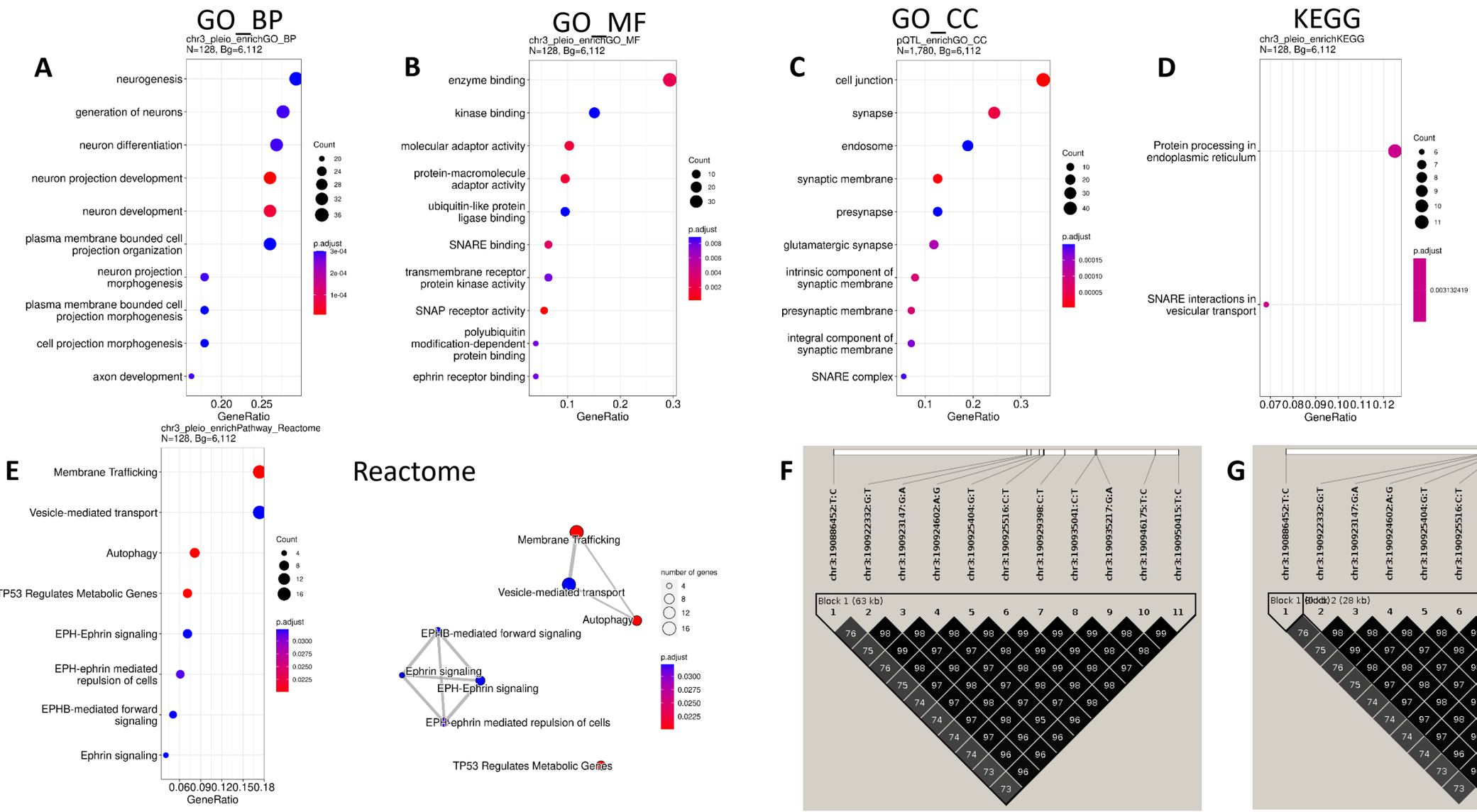




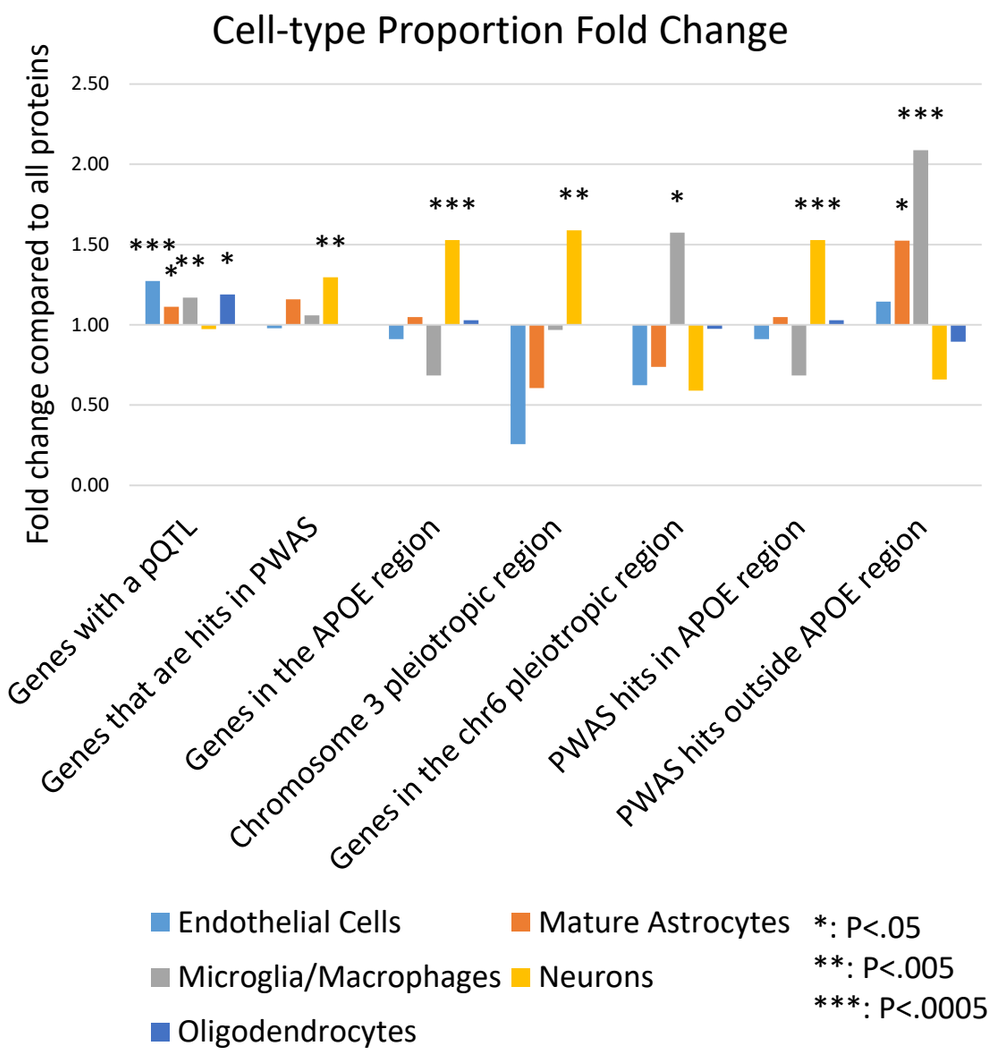
Supplementary Figure 8: Meta-analysis pQTL variant annotation. A. Variant annotation using VEP for all index pQTL variants, based on most severe annotation of any variant in LD (R^2 > 0.8). **B.** Variant annotation using VEP for all *cis* index pQTL variants. **C.** Variant annotation using VEP for all *trans* index pQTL variants. **D.** Variant annotation using VEP for all significant conditionally independent pQTL variants. **E.** Pearson correlation of absolute effect size of each conditionally independent pQTL variant with annotation severity from VEP. **F.** Pearson correlation of absolute effect size of each *cis* conditionally independent pQTL variant with annotation severity from VEP. **G.** Pearson correlation of absolute effect size of each *trans* conditionally independent pQTL variant with annotation severity from VEP.

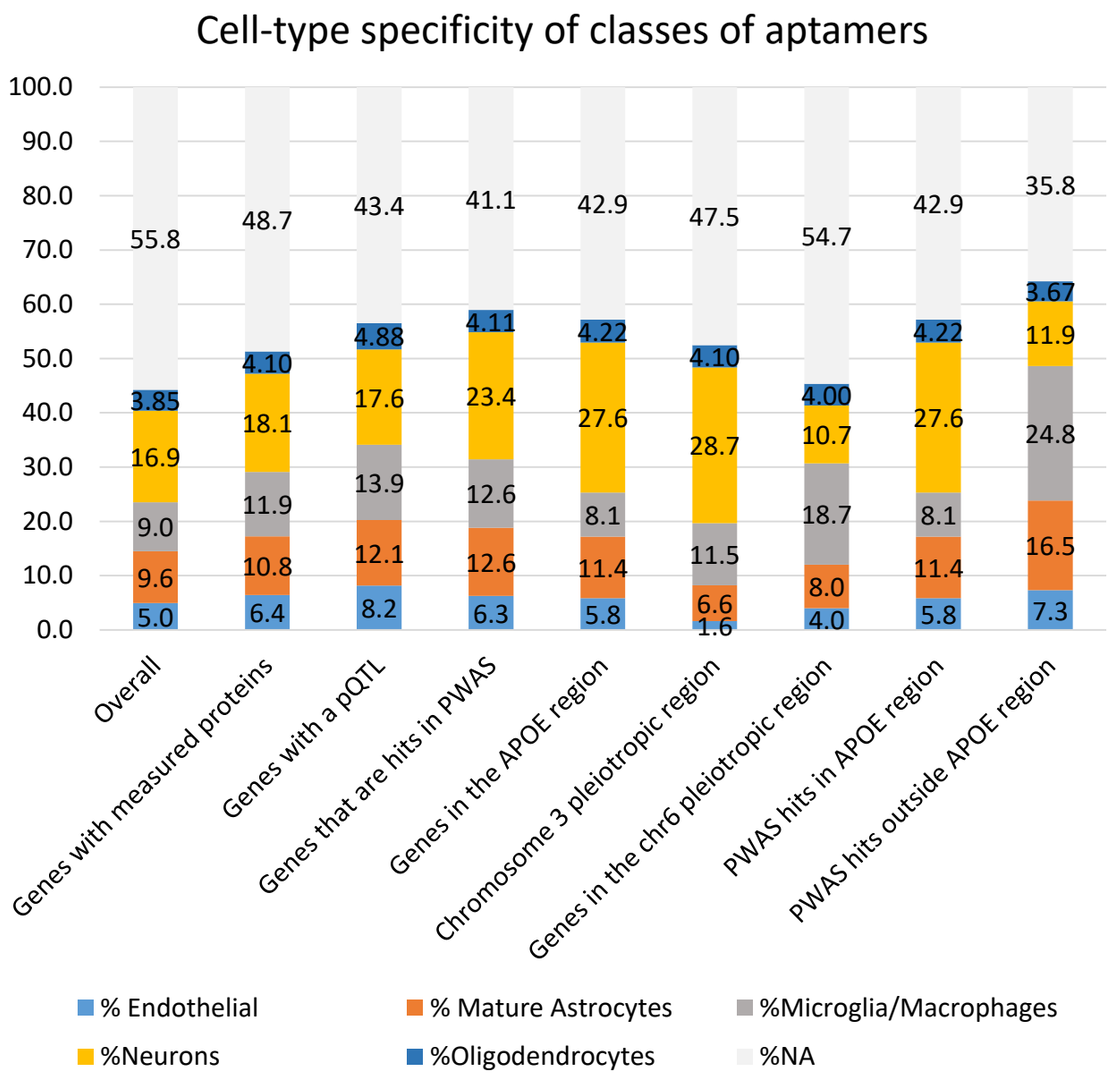


Supplementary Figure 9: Pathway enrichment analysis of all proteins with a significant QTL. A. Top enriched pathways for proteins with a pQTL compared to the full SOMAscan7k panel in Gene Ontology's biological processes. **B.** Top enriched pathways in Gene Ontology's molecular functions. **C.** Top enriched pathways in Gene Ontology's cellular components. **D.** Top enriched pathways in KEGG. **E.** Top enriched pathways and enrichment map from Reactome. **F.** Top enriched pathways and enrichment map from Disease Ontology.

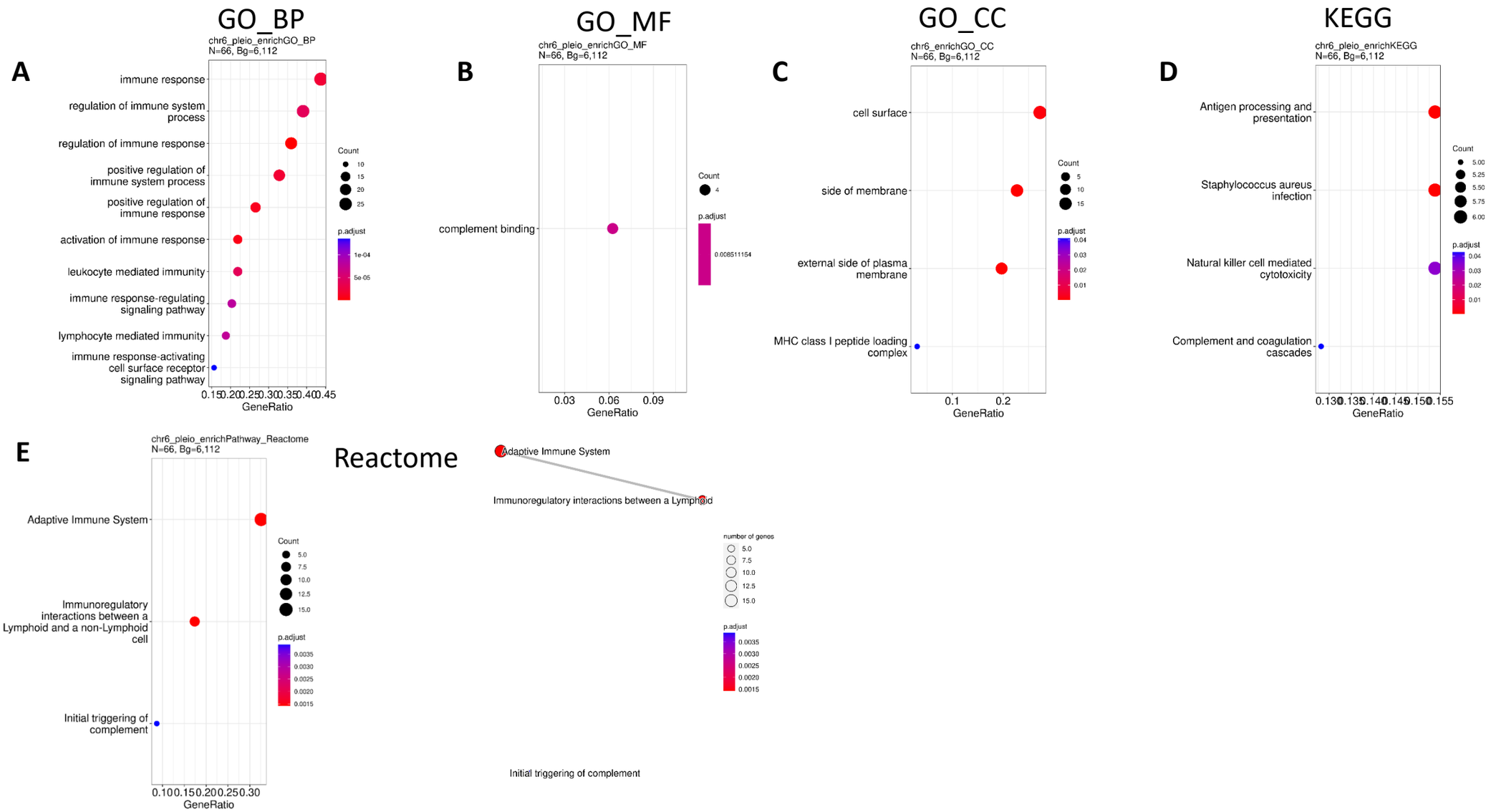


Supplementary figure 10: Pathway enrichment analysis of all proteins with a pQTL in the chromosome 3 pleiotropic region and Haploview plot of index pQTL variants in the region. A. Top enriched pathways for proteins with a pQTL in the chr3 pleiotropic region compared to the full SOMAscan7k panel in Gene Ontology's biological processes. **B.** Top enriched pathways in Gene Ontology's molecular functions. **C.** Top enriched pathways in Gene Ontology's cellular components. **D.** Top enriched pathways in KEGG. **E.** Top enriched pathways and enrichment map from Reactome. **F.** Haploview plot showing R^2 between index pQTL variants identified in this region. Blocks were defined using an R^2 threshold of 0.5. **G.** Haploview plot showing R^2 between index pQTL variants identified in this region. Blocks were defined using an R^2 threshold of 0.8.

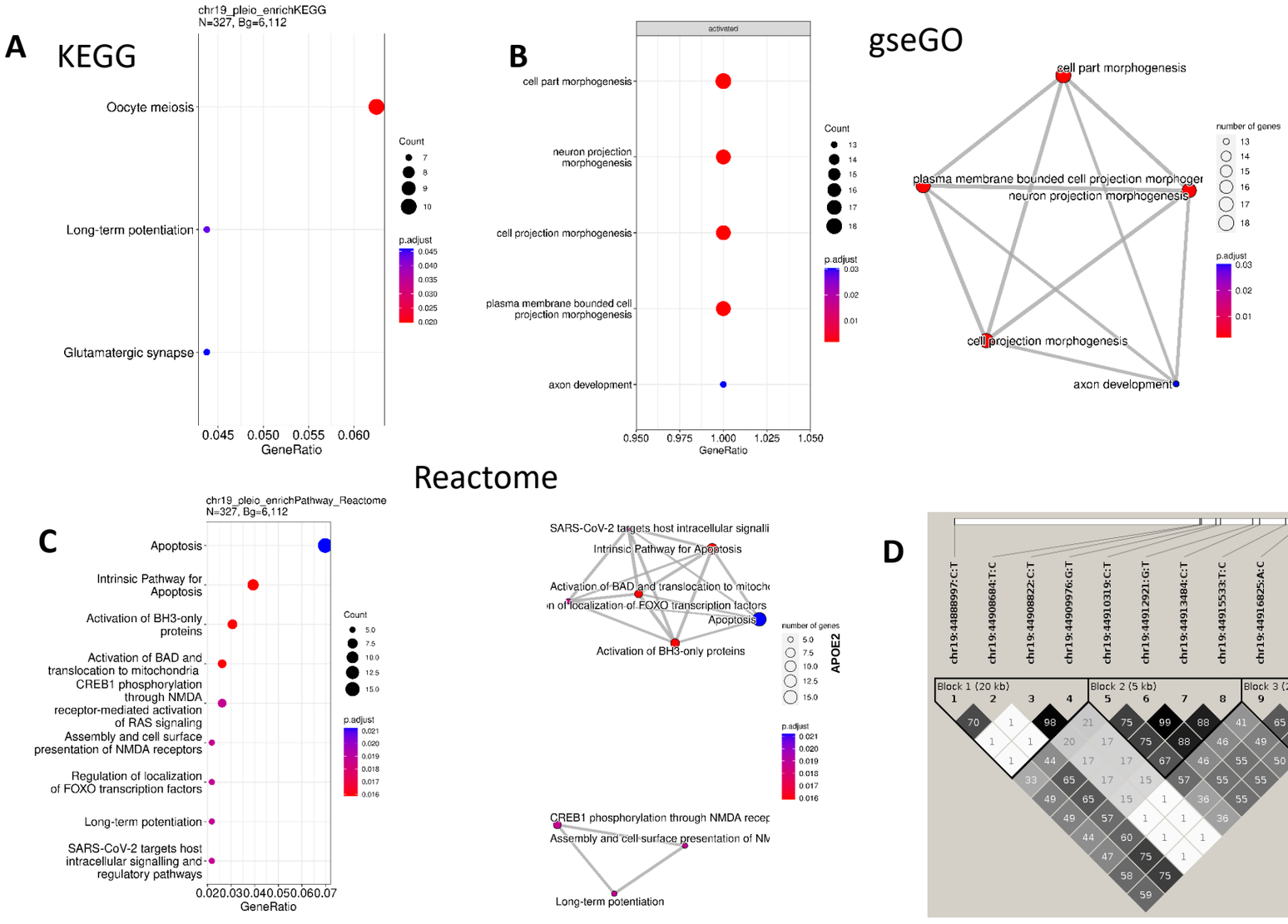




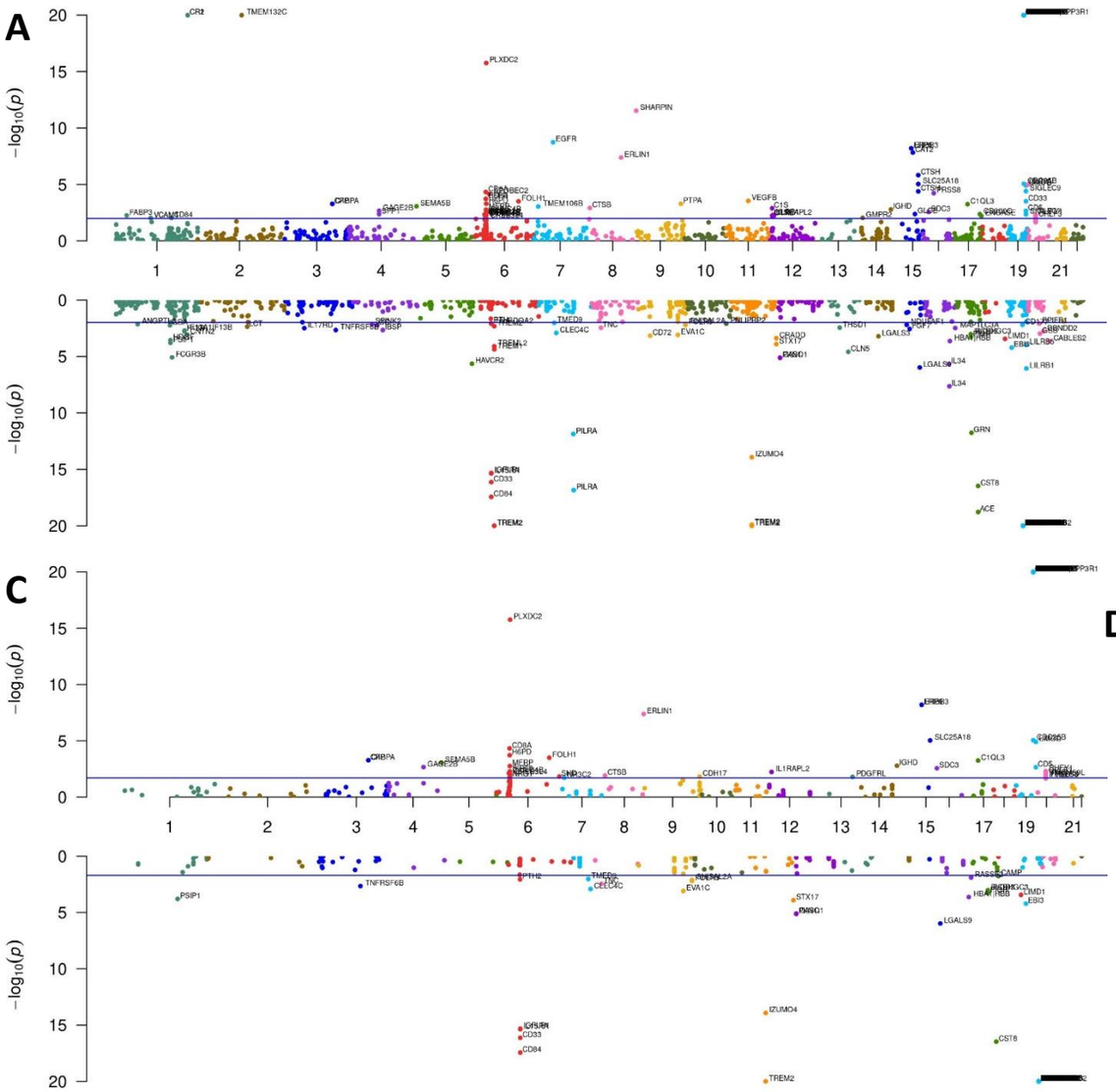
Supplementary Figure 11: Summary of brain cell-type specificity analysis. A. Cell-type enrichment fold change for subsets of proteins. All subsets were compared to the background set of genes whose proteins were measured in the SOMAscan7k panel. Fold change above 1: Enrichment for that cell type; fold change below 1: depletion for that cell type. P-values were calculated using the hypergeometric test. **B.** Percentage of each gene subset that is specific to each brain-relevant cell type.



Supplementary figure 12: Pathway enrichment analysis of all proteins with a pQTL in the chromosome 6 pleiotropic region. A. Top enriched pathways for proteins with a pQTL in the chr6 pleiotropic region compared to the full SOMAscan7k panel in Gene Ontology's biological processes. **B.** Top enriched pathways in Gene Ontology's molecular functions. **C.** Top enriched pathways in Gene Ontology's cellular components. **D.** Top enriched pathways in KEGG. **E.** Top enriched pathways and enrichment map from Reactome. **F.** Top enriched pathways and enrichment map from Disease Ontology.

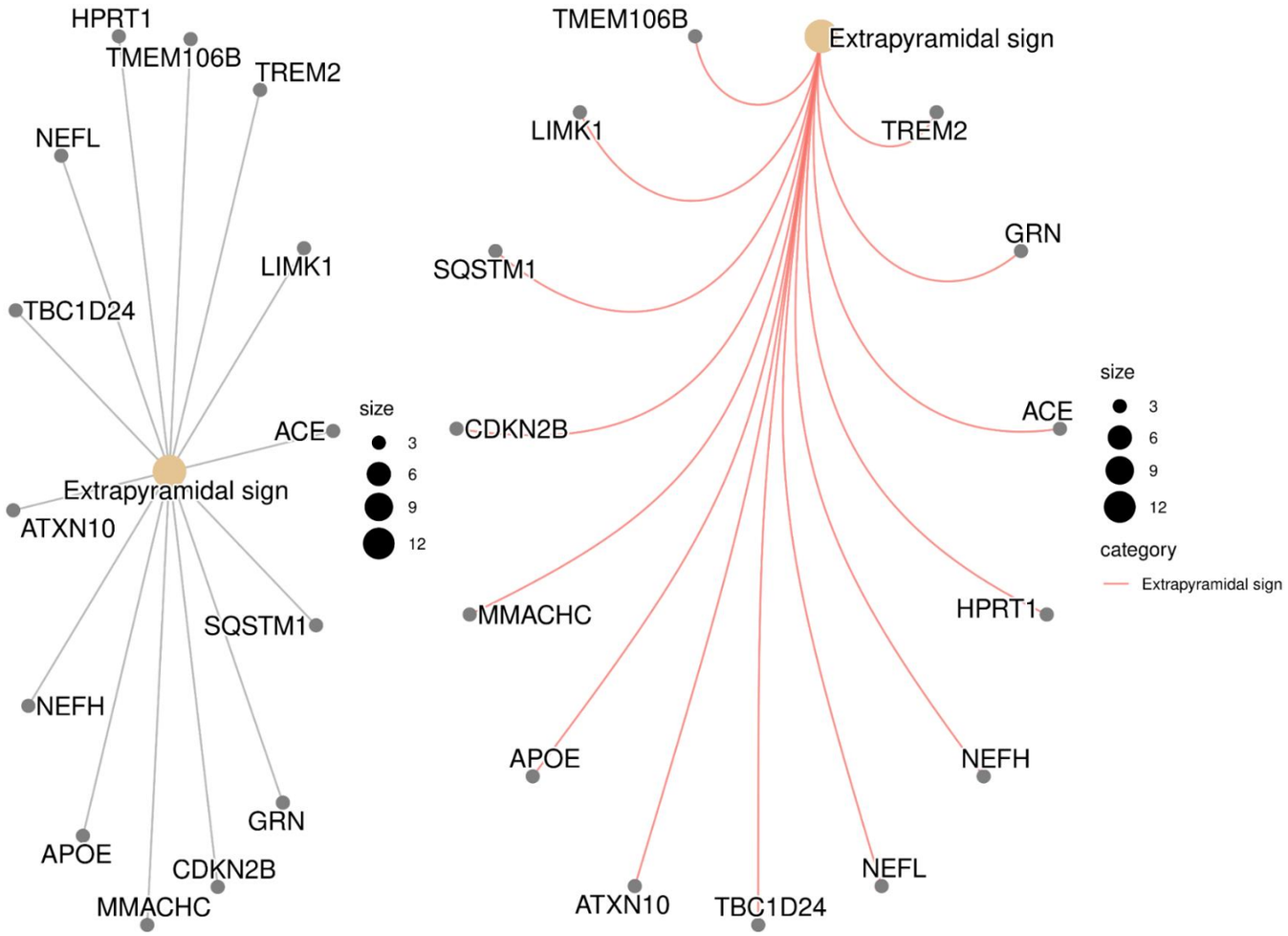


Supplementary figure 13: Pathway enrichment analysis of all proteins with a pQTL in the chromosome 19 pleiotropic region and Haploview plot if index pQTL variants in the region. A. Top enriched pathways for proteins with a pQTL in the chromosome 19 pleiotropic region compared to the full SOMAscan7k panel in KEGG. **B**. Top enriched pathways in Gene Ontology using the default gene background. **C**. Top enriched pathways in Reactome. **D**. Haploview plot showing R^2 between all index pQTL variants in the pleiotropic region. Blocks were determined through PLINK using the –indep-pairwise flag using an R^2 cutoff of 0.5. **E**. Haploview plot showing R^2 between all index pQTL variants in the pleiotropic region. Blocks were determined through PLINK using the –indep-pairwise flag using an R^2 cutoff of 0.8.

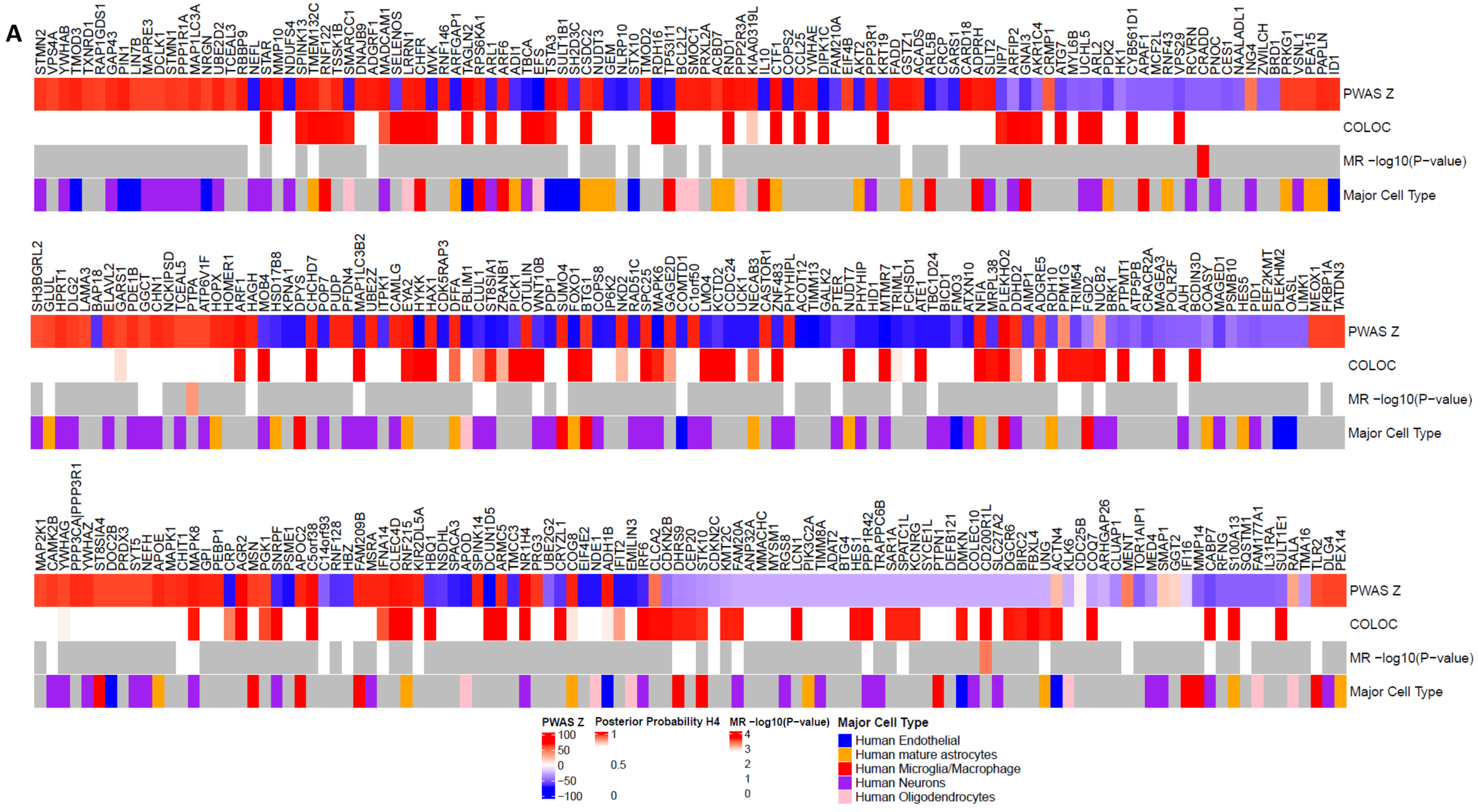


Supplementary Figure 14: PWAS Plots. A. Miami plot of all significant associations in PWAS (*cis* and *trans*). Proteins are plotted according to the location of the index pQTL variant in the association region. Blue line is B&H FDR-corrected p-value threshold (P = 0.0104). Top: positive PWAS z-scores. Bottom: negative PWAS z-scores. **B.** Miami plot of all significant *cis* associations through PWAS. Blue line is same B&H FDR-corrected p-value threshold as full plot. **C.** Miami plot of all significant *trans* associations through PWAS. Blue line is same B&H FDR-corrected p-value threshold as full plot. **D.** 2D Manhattan plot of all significant PWAS associations. **E.** Volcano plot of PWAS Z-scores. Red line is B&H FDR-corrected p-value threshold. Proteins are colored by their specific brain-relevant cell type.

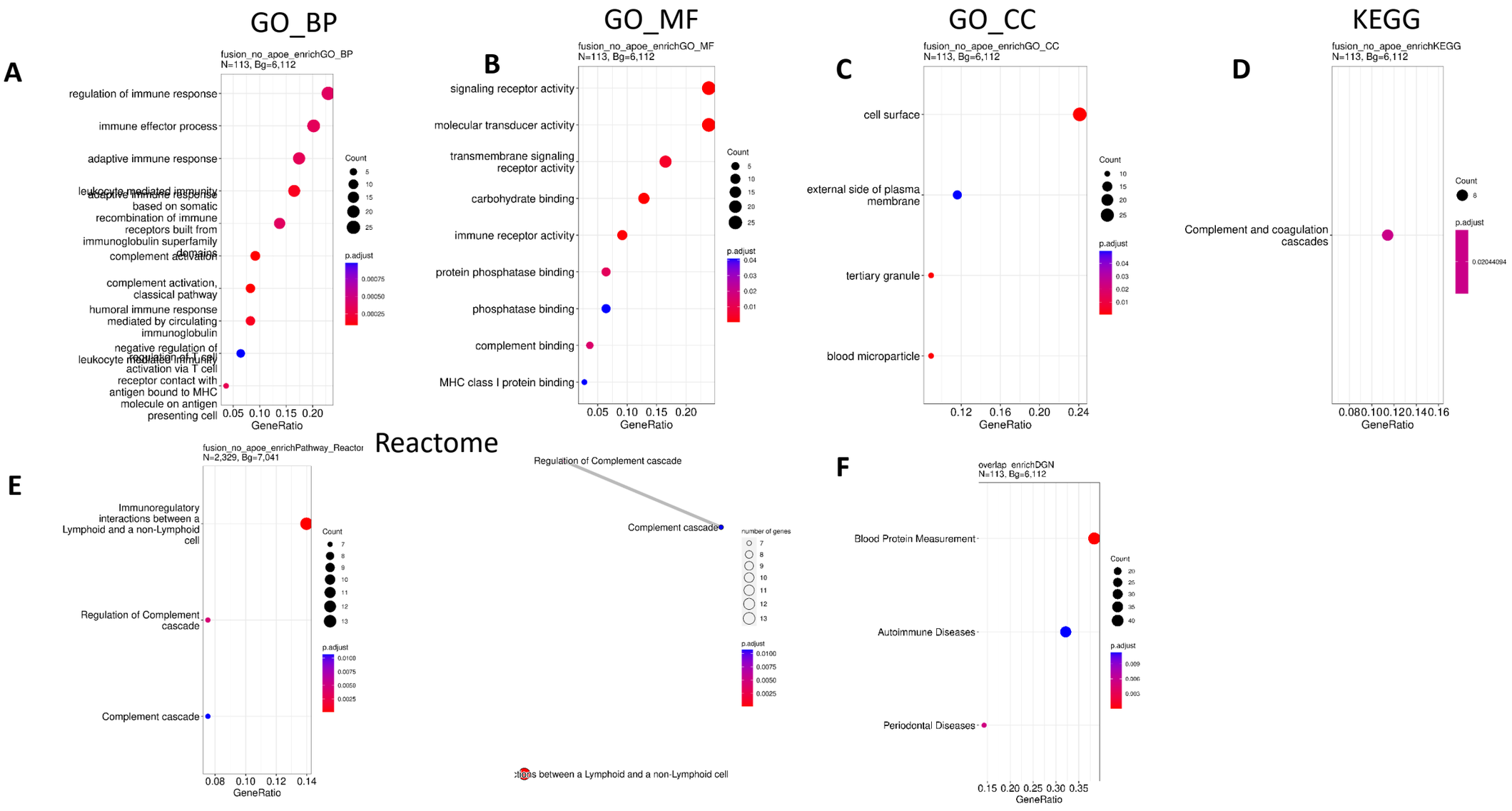
A



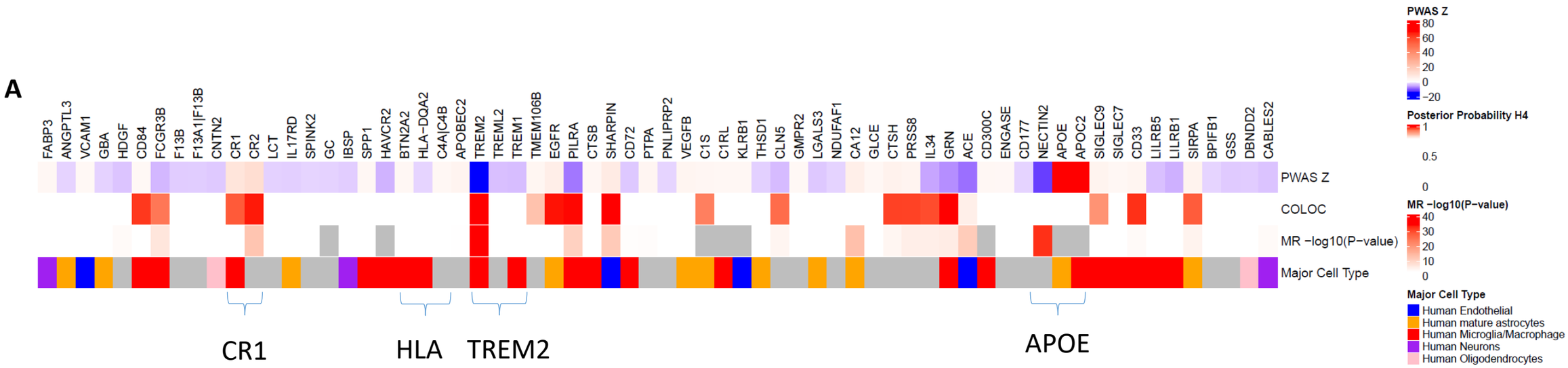
Supplementary Figure 15: Pathway enrichment analysis for all proteins that were significant in PWAS. A. Top enriched pathways and enrichment map from DisGeNet.



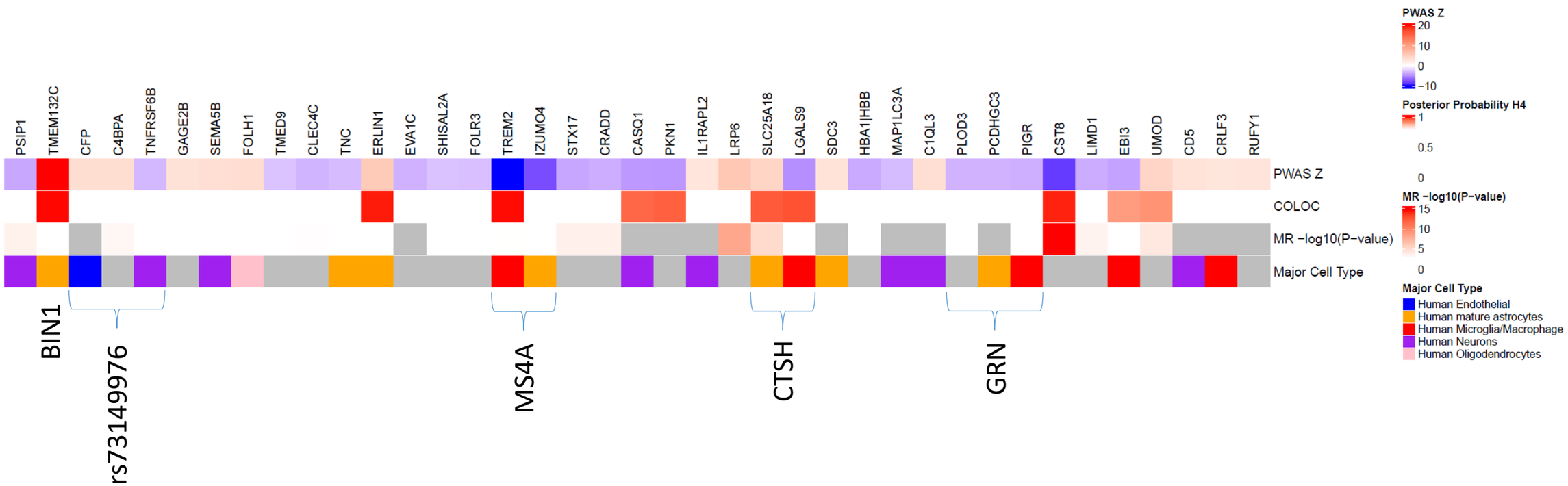
Supplementary Figure 16: Characterization of all APOE-region pQTLs significant through PWAS. A. Details of all proteins with a pQTL in the chromosome 19 pleiotropic region that are significant through PWAS. PWAS Z: Z-score for the association between protein level and AD. COLOC: Posterior probability of a shared causal variant between the pQTL and AD. MR –log10(P-value): P-value for the association between protein and AD through Mendelian randomization. Major Cell Type: Predominant brain-relevant cell type for each protein.



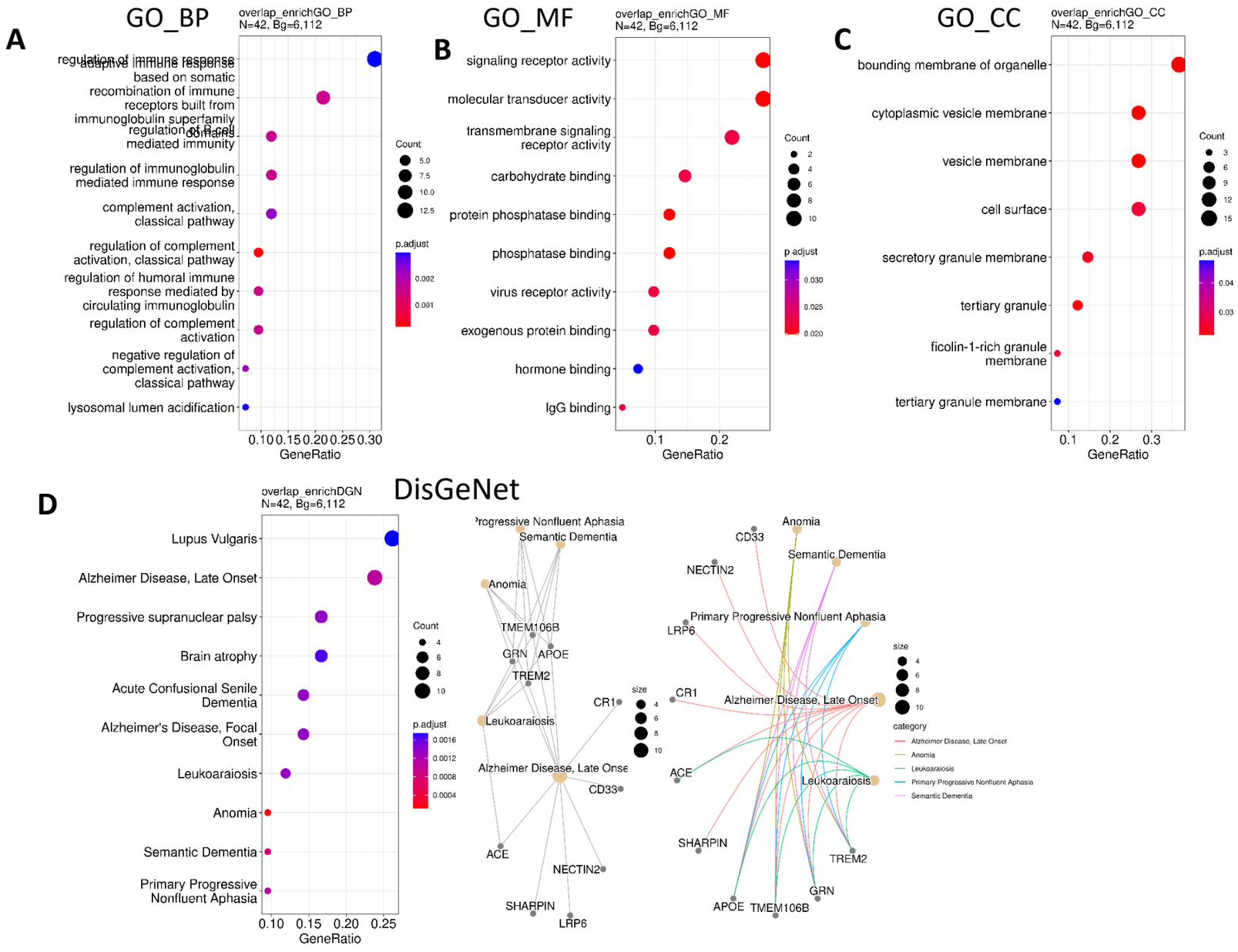
Supplementary Figure 17: Pathway enrichment analysis for all proteins (excl APOE region) that were significant in PWAS. A. Top enriched pathways for PWAS-significant proteins (excluding the *APOE* pleiotropic region) compared to the full SOMAscan7k panel in Gene Ontology's biological processes. **B.** Top enriched pathways in Gene Ontology's molecular functions. **C.** Top enriched pathways in Gene Ontology's cellular components. **D.** Top enriched pathways in KEGG. **E.** Top enriched pathways and enrichment map from Reactome. **F.** Enriched pathways in DisGeNet.



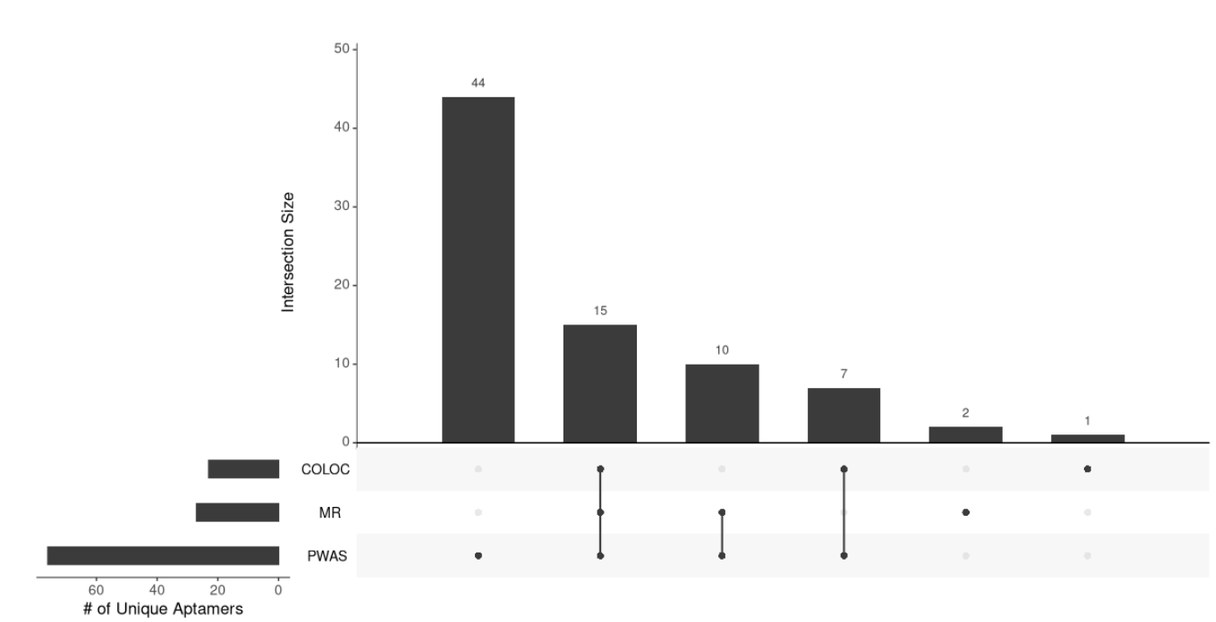
Supplementary Figure 18: Characterization of all *cis*-pQTLs significant through PWAS. A. Details of all proteins with a *cis*-pQTL that are significant through PWAS. PWAS Z: Z-score for the association between protein level and AD. COLOC: Posterior probability of a shared causal variant between the pQTL and AD. MR Z: Z-score for the association between protein and AD through Mendelian randomization. Major Cell Type: Predominant brain-relevant cell type for each protein.

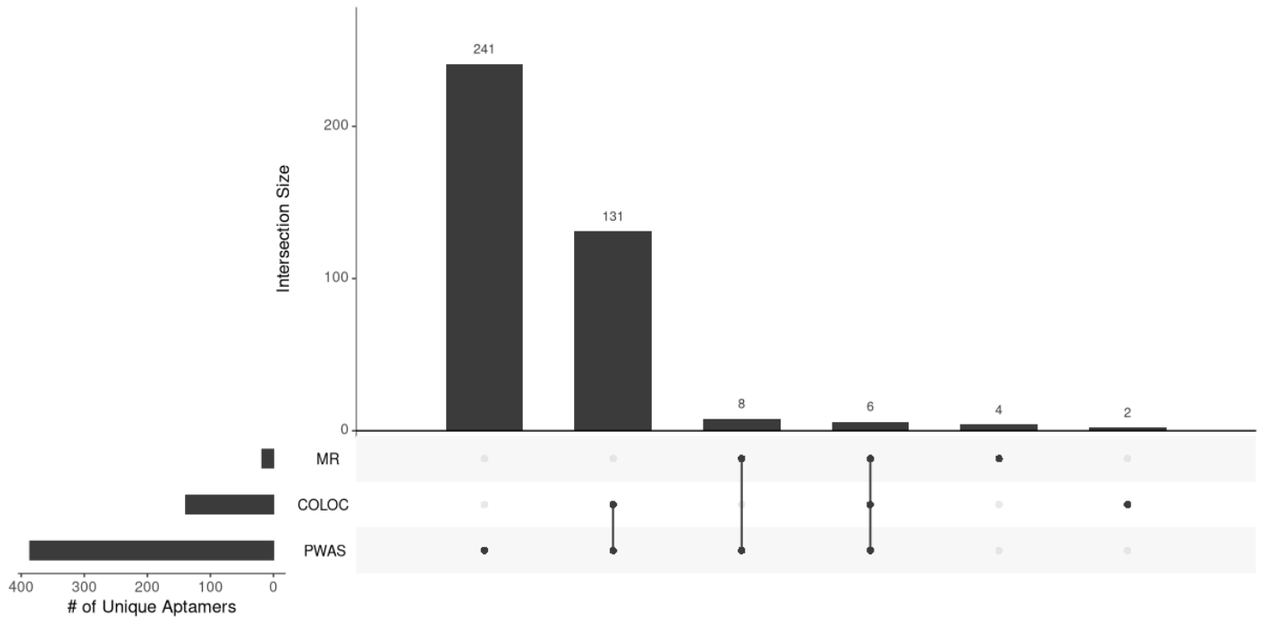


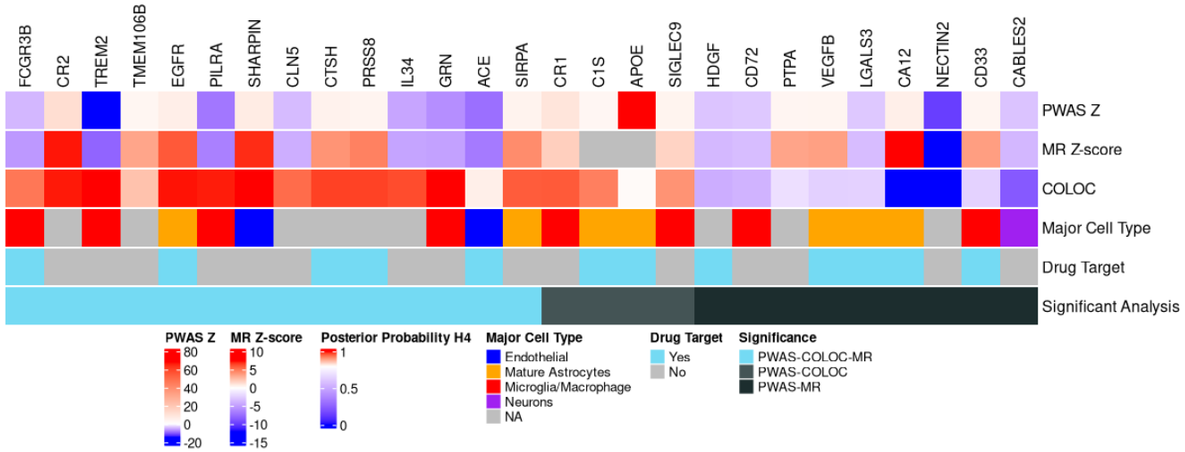
Supplementary Figure 19: Characterization of all trans pQTLs (excluding APOE region and MHC region) significant through PWAS. A. Details of all proteins with a *trans*-pQTL outside the chromosome 19 pleiotropic region that are significant through PWAS. PWAS Z: Z-score for the association between protein level and AD. COLOC: Posterior probability of a shared causal variant between the pQTL and AD. MR –log10(P): Z-score for the association between protein and AD through Mendelian randomization. Major Cell Type: Predominant brain-relevant cell type for each protein.



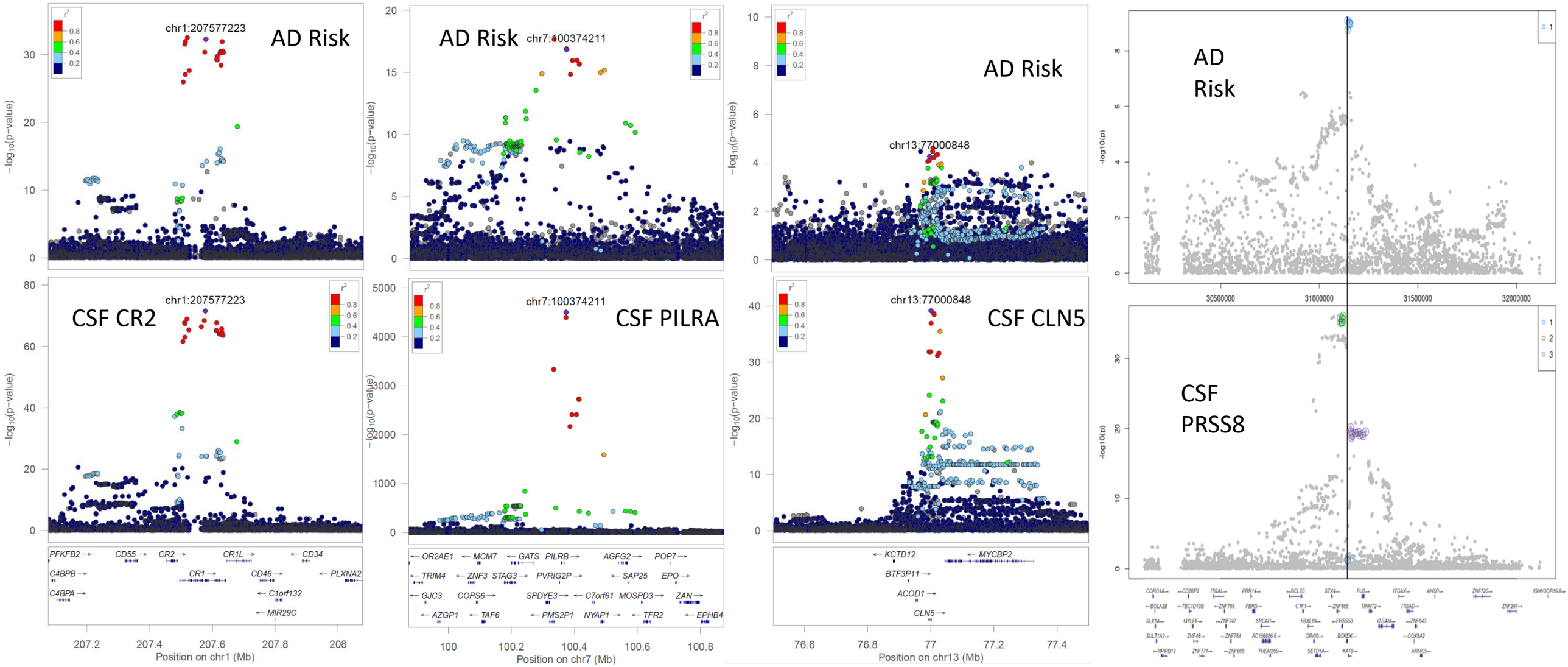
Supplementary Figure 20: Pathway Enrichment analysis of proteins that overlapped between at least two of PWAS, COLOC, and MR. A. Top enriched pathways for proteins that are significant in at least two of PWAS, COLOC, and MR for AD compared to the full SOMAscan7k panel in Gene Ontology's biological processes. **B.** Top enriched pathways in Gene Ontology's molecular functions. **C.** Top enriched pathways in Gene Ontology's cellular components. **D.** Top enriched pathways and enrichment map from DisGeNet.



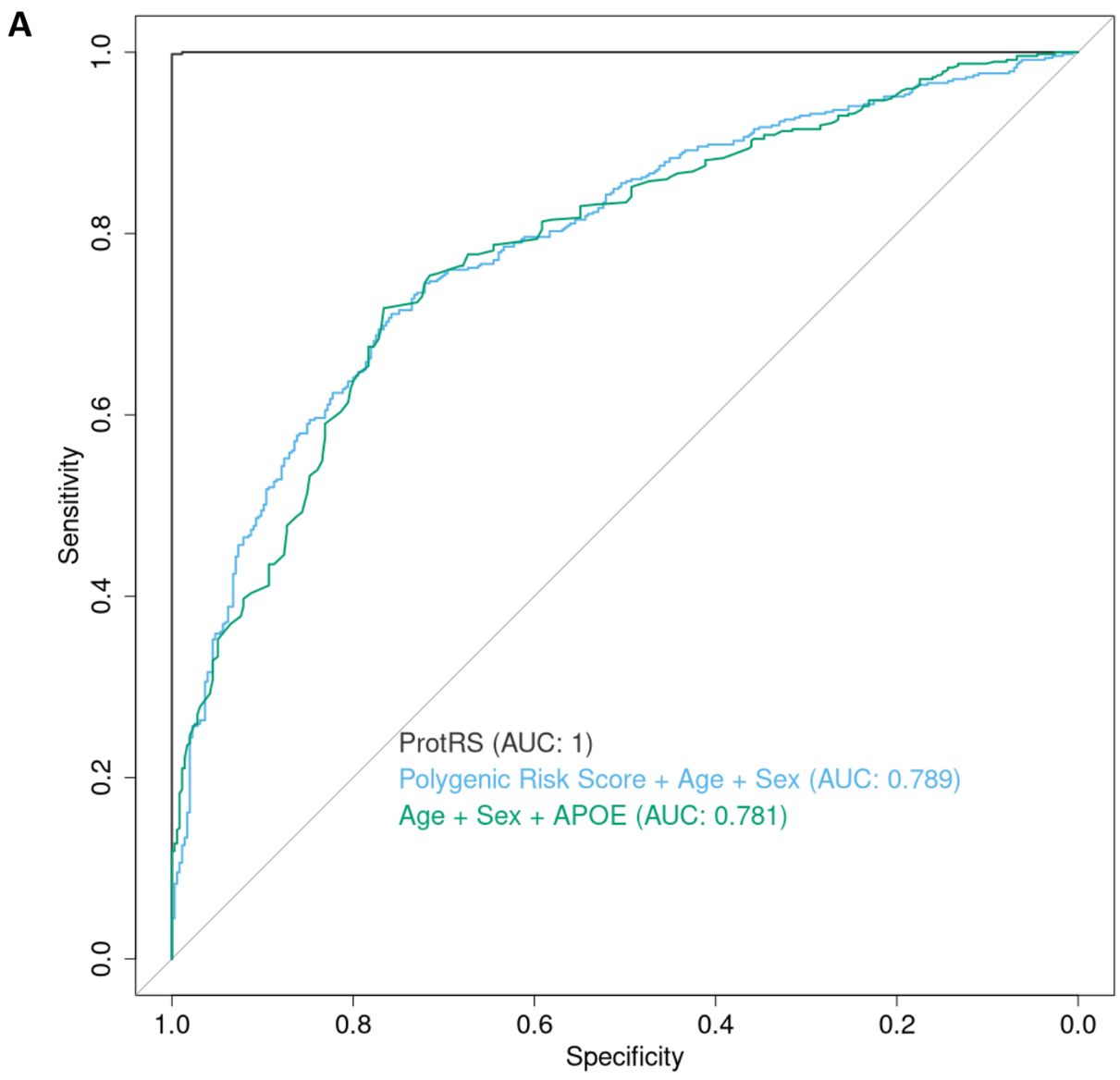




Supplementary Figure 21: Overlap between PWAS, COLOC, and MR for cis & trans associations. A. Upset plot showing the overlap of aptamers significant for at least one of PWAS, COLOC, and MR including only *cis*-pQTL associations. **B.** Upset plot showing overlap between aptamers significant for at least one of PWAS, COLOC, and MR through their *trans*-pQTL. **C.** Description of the proteins that overlap between at least two of PWAS, colocalization, and MR using *cis*-only pQTL associations. PWAS Z & MR Z: red represents positive Z-score, blue represents negative z-score. COLOC: color represents posterior probability of sharing a genetic signal between pQTL and AD (Red: PP.H4 > 0.8; blue: PP.H4 < 0.8). Major cell type: Predominant brain-relevant cell type for proteins of interest. Drug Target: Proteins targeted by a molecule as described in the DrugBank database. Significant Analysis: Of PWAS, COLOC, and MR, light blue corresponds to reaching inclusion threshold in all three; gray corresponds to reaching inclusion threshold in only PWAS & COLOC, black corresponds to reaching inclusion threshold in only PWAS and MR.



Supplementary Figure 22: Local plots of selected pQTL signals. A. Local plots showing the association with AD and with CR2 protein levels at chr1:207577223. **B.**Local plots showing the association with AD and with PILRA protein levels at chr7:100374211. **C.** Local plots showing the association with AD and with CLN5 protein levels at chr13:7700848. **D.** Local plots showing the association with AD and three credible sets of causal variants associated with PRSS8 protein levels. The index AD variant in this region is at chr16:31111250.



Supplementary Figure 23: Proteomic risk score analysis using all PWAS-associated proteins. A. Receiver-operator characteristic curve for prediction of AT-status in the training dataset. N(A+T+) = 471; N(AT-) = 355. Black: model including proteomic risk score from 456 aptamers. Blue: model including polygenic risk score calculated using PRSice with AD-associated variants at $P < 5\times10^{-8}$ (incl. *APOE* region) with age and sex. Green: model including age, sex, and *APOE* genotype. **C.** ROC curves for *APOE* genotype-stratified prediction of AT-status. All ProtRS ROC curves shown were calculated using the proteomic risk score calculated from 456 aptamers, age, and sex. **D.** ROC curves for age-stratified prediction of AT-status. All ProtRS ROC curves shown were calculated using the proteomic risk score calculated from 456 aptamers and sex.