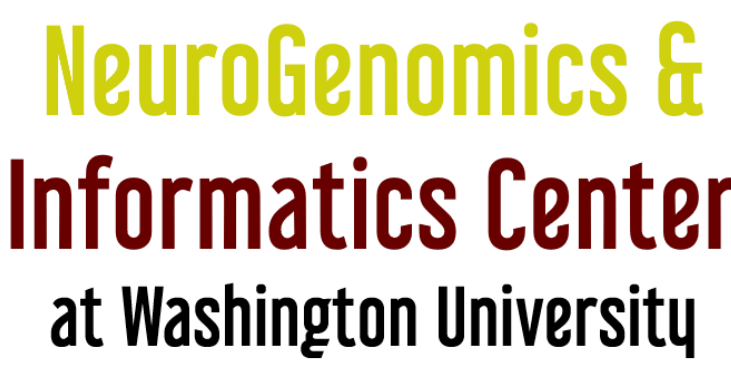


Low Overlap of Plasma and CSF protein quantitative trait loci affects protein discovery for neurological disease



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Background

- Quantitative trait loci (QTLs) have become a vital component of understanding disease GWAS loci¹.
- Most protein QTL analyses have focused on plasma^{2,3}, which may be less relevant to neurological diseases than a fluid like cerebrospinal fluid (CSF).
- We compared plasma and CSF pQTL datasets to determine which showed greater relevance for gene discovery for 14 neurological diseases.

Study Overview & Methods

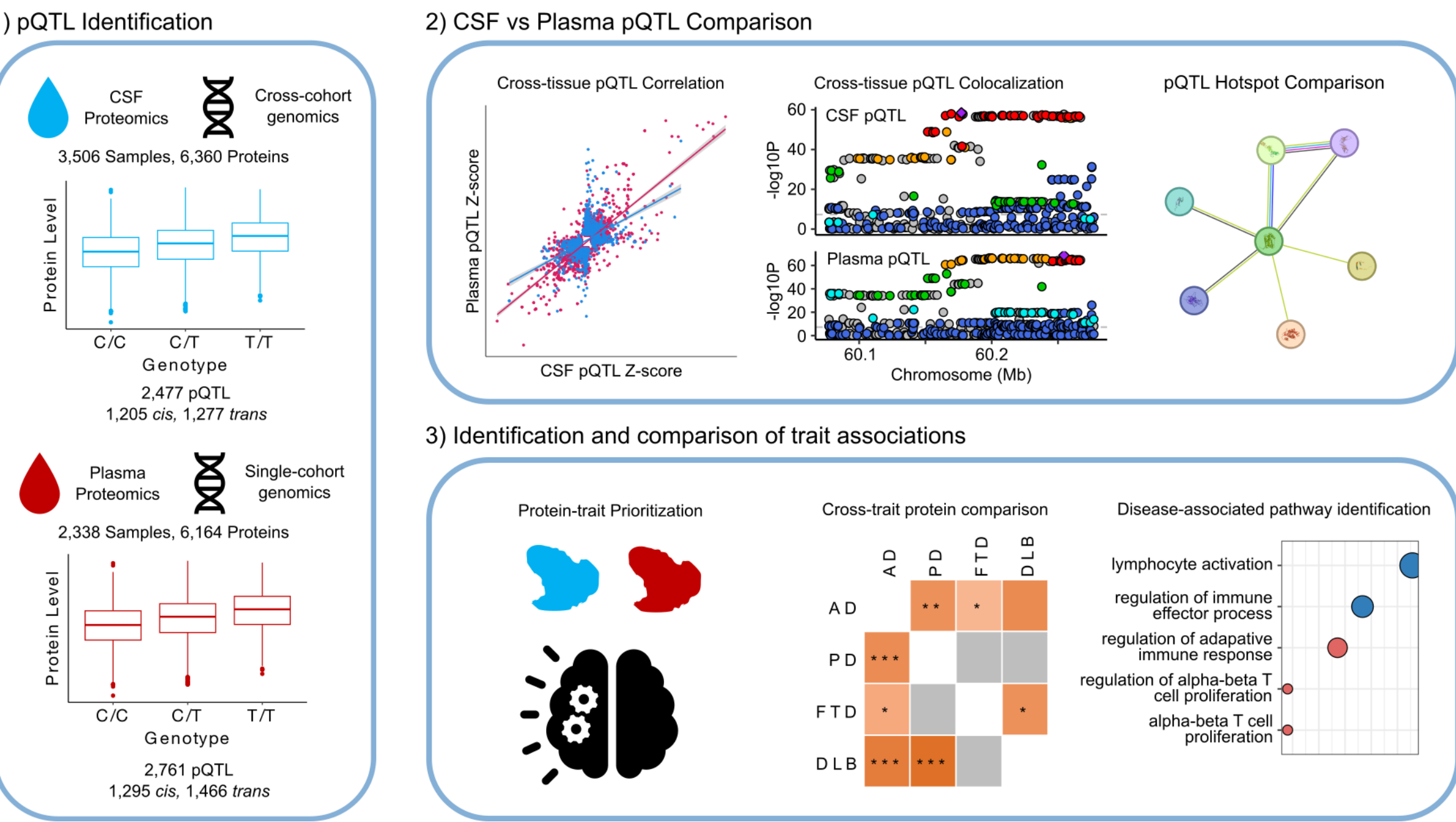


Figure 1. Overview of analyses.

- We integrated CSF and plasma pQTL datasets with neurological disease GWAS through colocalization, Mendelian Randomization, and proteome-wide association study (PWAS).
- We identified significant trait correlations using RHOGE.
- We used fluid-specific pathway analysis to identify disease mechanisms with differing detection between CSF and plasma.
- We identified specific proteins contributing to fluid-specific pathways.

Conclusions

- Thousands of pQTLs were present in CSF and plasma, but the fluids differed substantially in the specifics
- The fluids had very little overlap in disease-associated proteins, suggesting they capture different information
- CSF proteins showed greater disease relevance based on pathway analysis than plasma proteins
- Increased context-specific pQTLs will expand our knowledge of disease-associated genetic variation

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Manuscript: <https://doi.org/10.1126/scitranslmed.adz2016>

Results

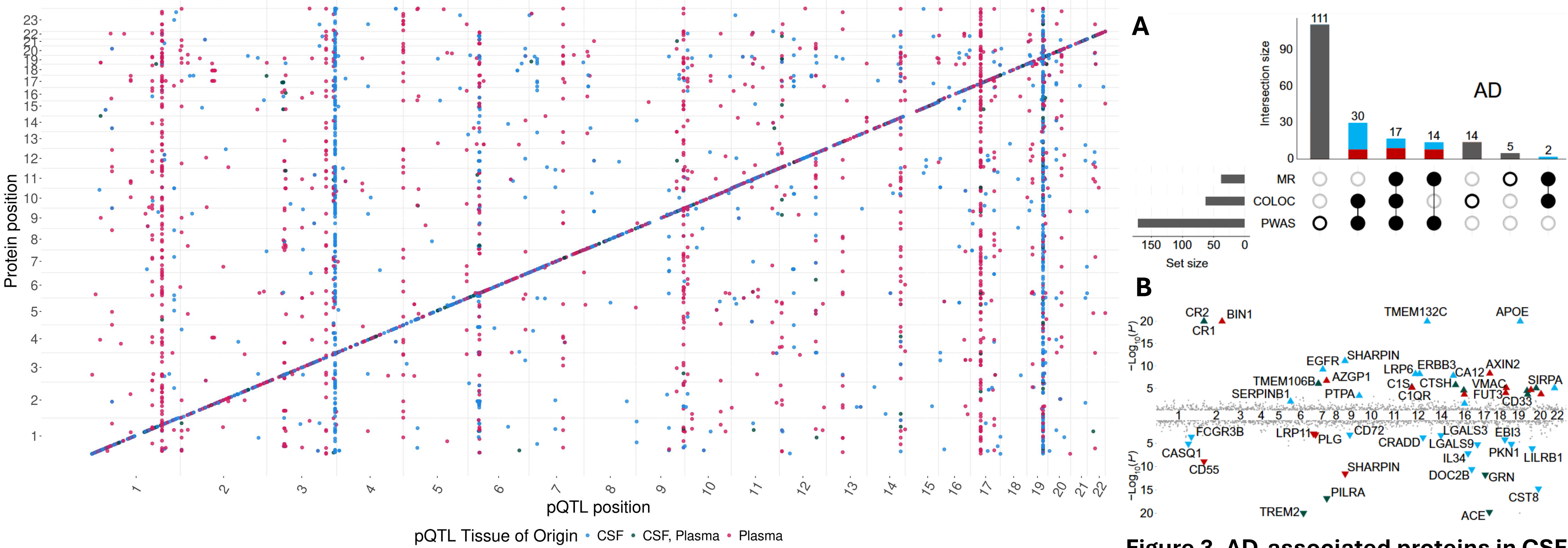


Figure 2. pQTL Distributions between CSF & Plasma. X-axis, location of variation associated with protein abundance. Y-axis, location of protein-coding gene.

Figure 3. AD-associated proteins in CSF & plasma. A, UpSet plot of AD-associated proteins through each of three methods. B, Miami plot of PWAS p-values for each protein, split by the fluid of origin (red, plasma; blue, CSF; green, both).

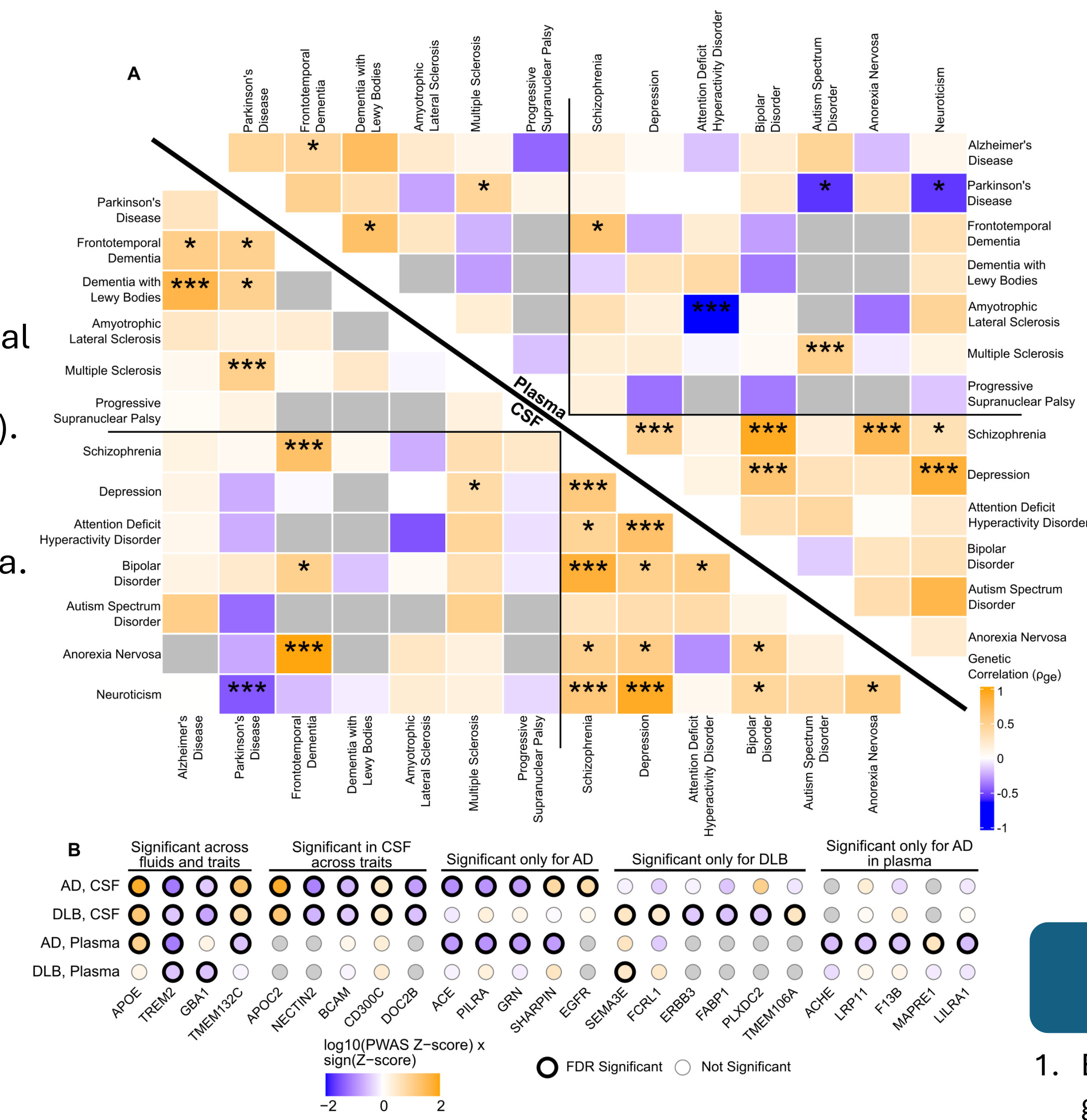
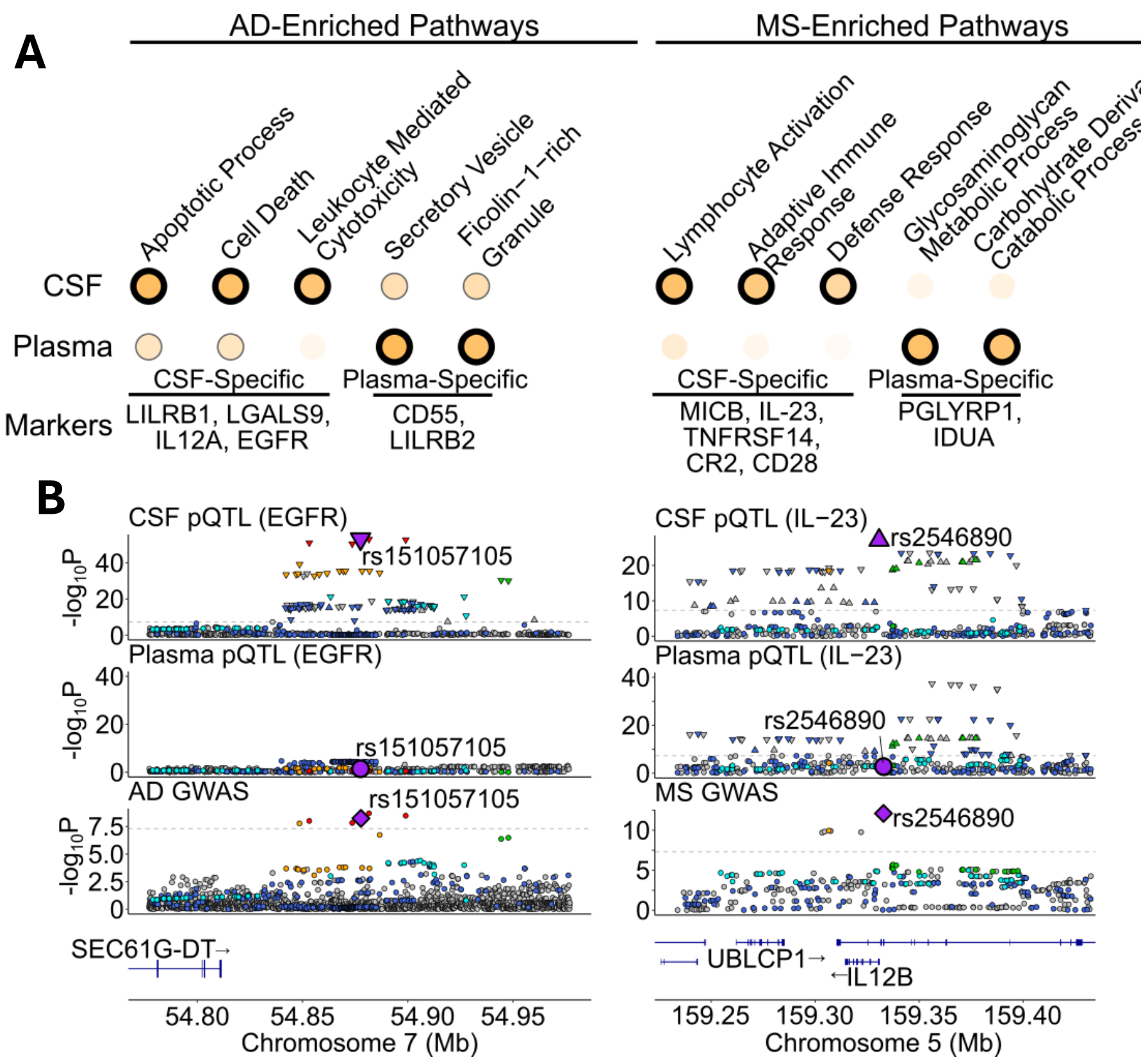


Figure 4. Trait correlations mediated by pQTL results in CSF & plasma. A, Trait correlations as identified by RHOGE. *, $P < 0.05$; ***, $FDR < 0.05$. B, Proteins driving the significant AD-DLB correlation, split by CSF & plasma statistics for significant associations with each trait.

Figure 5. Differential pathways between CSF & plasma. A, Fluid-specific pathways for Alzheimer's & Multiple Sclerosis-associated proteins. B, Local GWAS plots of EGFR (AD) and IL-23 (MS) pQTLs in each fluid with disease GWAS results.



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