

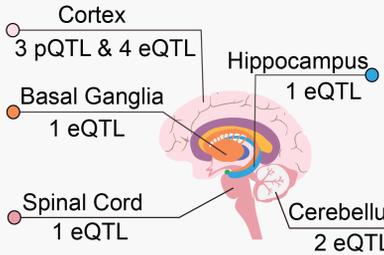
# Supplementary Figure 1

## Workflow of Mendelian Randomization (MR) in Alzheimer's Disease

### Instrument Variables (IVs)



Brain region pQTL/eQTL



pQTL [Cortex-ROSMAP.All  
Cortex-ROSMAP.CtI  
Cortex-Banner  
Cortex-ROSMAP  
Cortex-Mayo  
Cortex-Metabrain  
Cortex+Cerebellum  
-Multi-centers  
eQTL [Cerebellum-Mayo  
Cerebellum-Metabrain  
BasalGanglia-Metabrain  
Hippocampus-Metabrain  
SpinalCord-Metabrain



Celltype eQTLs

[Microglia-Fujita  
Microglia.MFG-Lopes  
Microglia.STG-Lopes  
Astrocytes-Fujita  
Astrocytes-Bryois  
Excitatory Neurons-Fujita  
Inhibitory Neurons-Fujita  
OPC-Fujita  
Oligodendrocytes-Fujita

Exposure: 20,320 Genes

$\beta_{MR}$

Outcomes



GWAS datasets  
(cases - controls)

### Criteria to select high-confidence IVs

- FDR < 0.05
- F-statistic > 10,  $F = \beta^2/se^2$
- Linkage disequilibrium (LD) clumping,  $r^2 < 0.2$
- One significant IV associate with one gene



[AD / proxy-AD (85,934 ~ 401,577) — Bellenguez, 2022  
AD.NoUKB23me (39,918 ~ 358,140) — Wightman, 2021  
AD / proxy-AD (75,024 ~ 397,844) — Schwartzentruber, 2021  
proxy-AD (53,042 ~ 355,900)  
AD / proxy-AD (71,880 ~ 383,378) — Jansen, 2019  
AD (71,880 ~ 383,378) — Kunkle, 2019



[PD/proxy-PD (22,632 ~ 968,735) — Nalls, 2022  
PD.No23me (42,792 ~ 568,693) — Kim, 2021



[ALS (29,612 ~ 122,656) — van Rheenen, 2021

### MR approaches

- $n_{IV} = 1$  → MR - Wald ratio (Performed for all SNPs)
- $n_{IV} = 2$  → MR - Inverse-variance weighted (IVW)
- $n_{IV} \geq 3$  → MR - IVW  
MR - Maximum likelihood (MaxLik)  
MR - Weighted Median (iteration = 10,000)  
MR - MR-presso  
Heterogeneity test  
Cochran's Q,  $I^2 < 0.5$   
Outlier correction

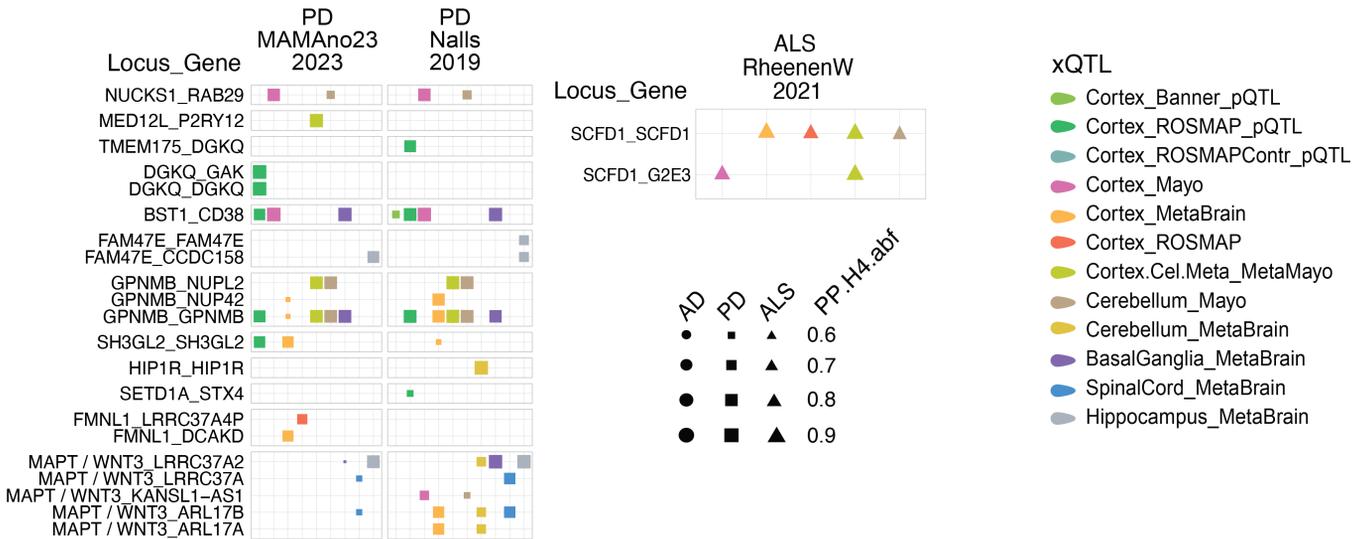
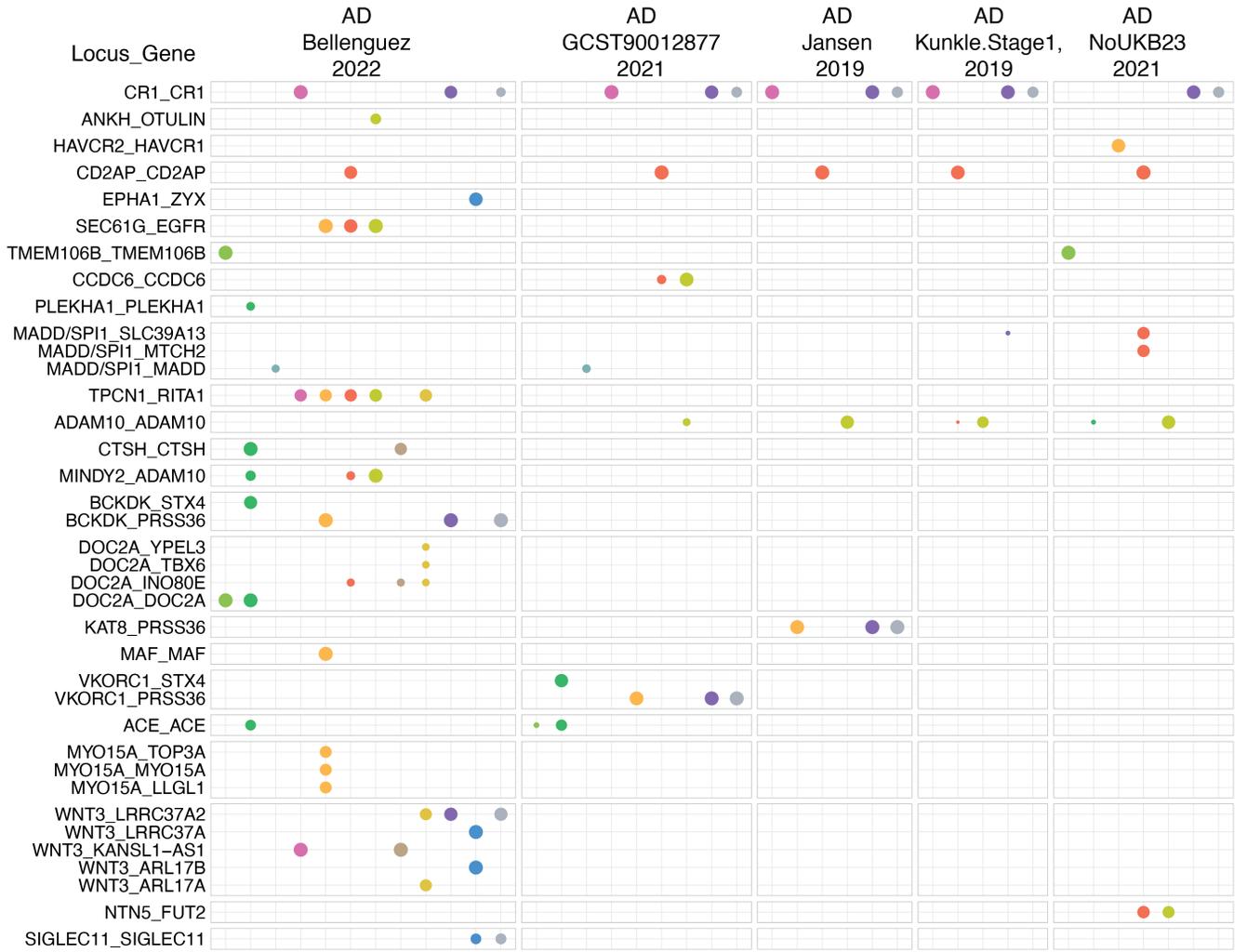
### alzMR-score

$$\text{alzMR}(g) = \sum_j \sum_k Z_{jkg}$$

Z, Z-statistic  
 $k = 1, \dots, K$  (  $k$ th QTLs )  
 $j = 1, \dots, J$  (  $j$ th AD-GWAS )  
 $g = 1, \dots, G$  (  $g$ th target )

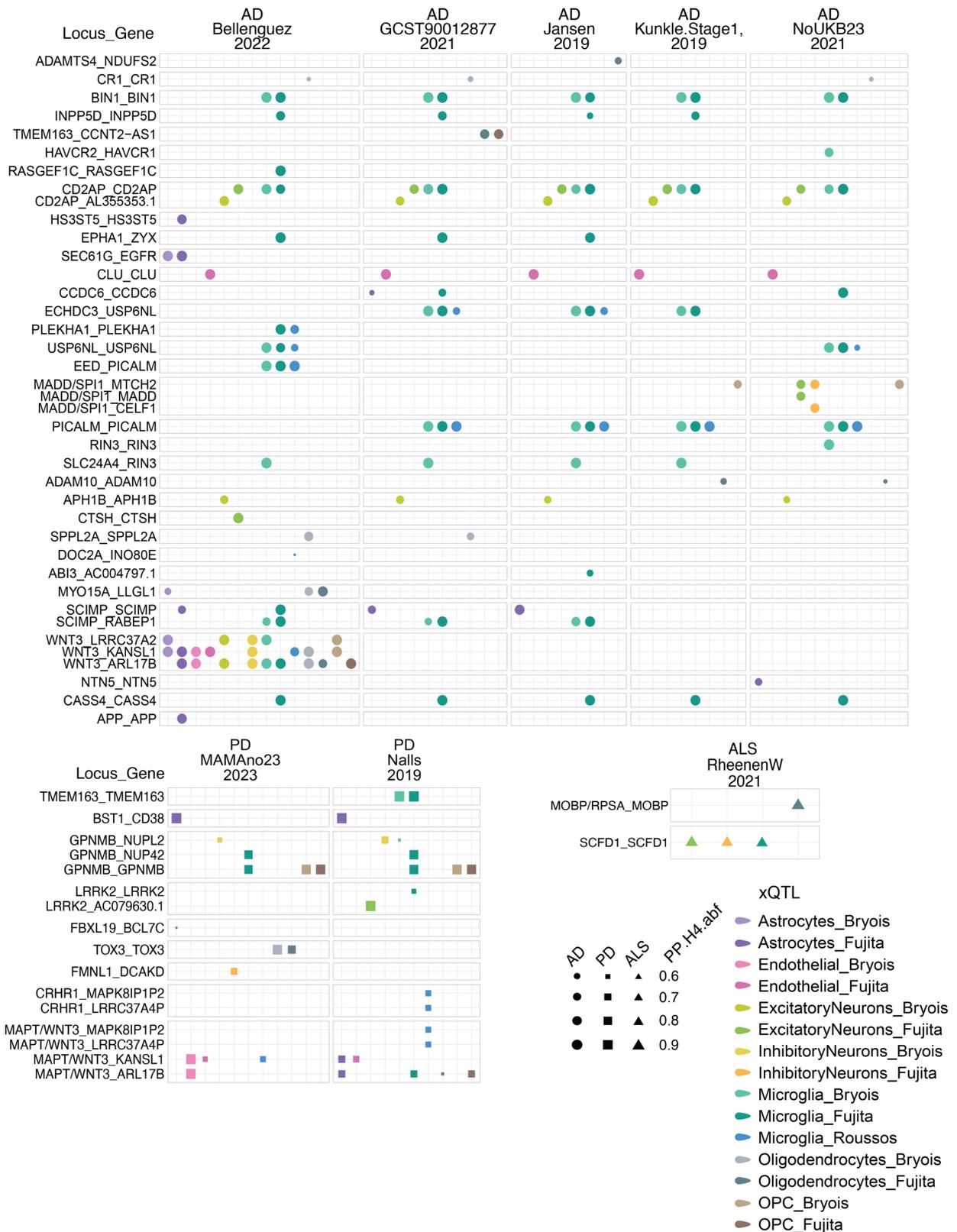
**Supplementary Figure 1. Workflow of Mendelian Randomization (MR) analysis across Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).**

# Supplementary Figure 2



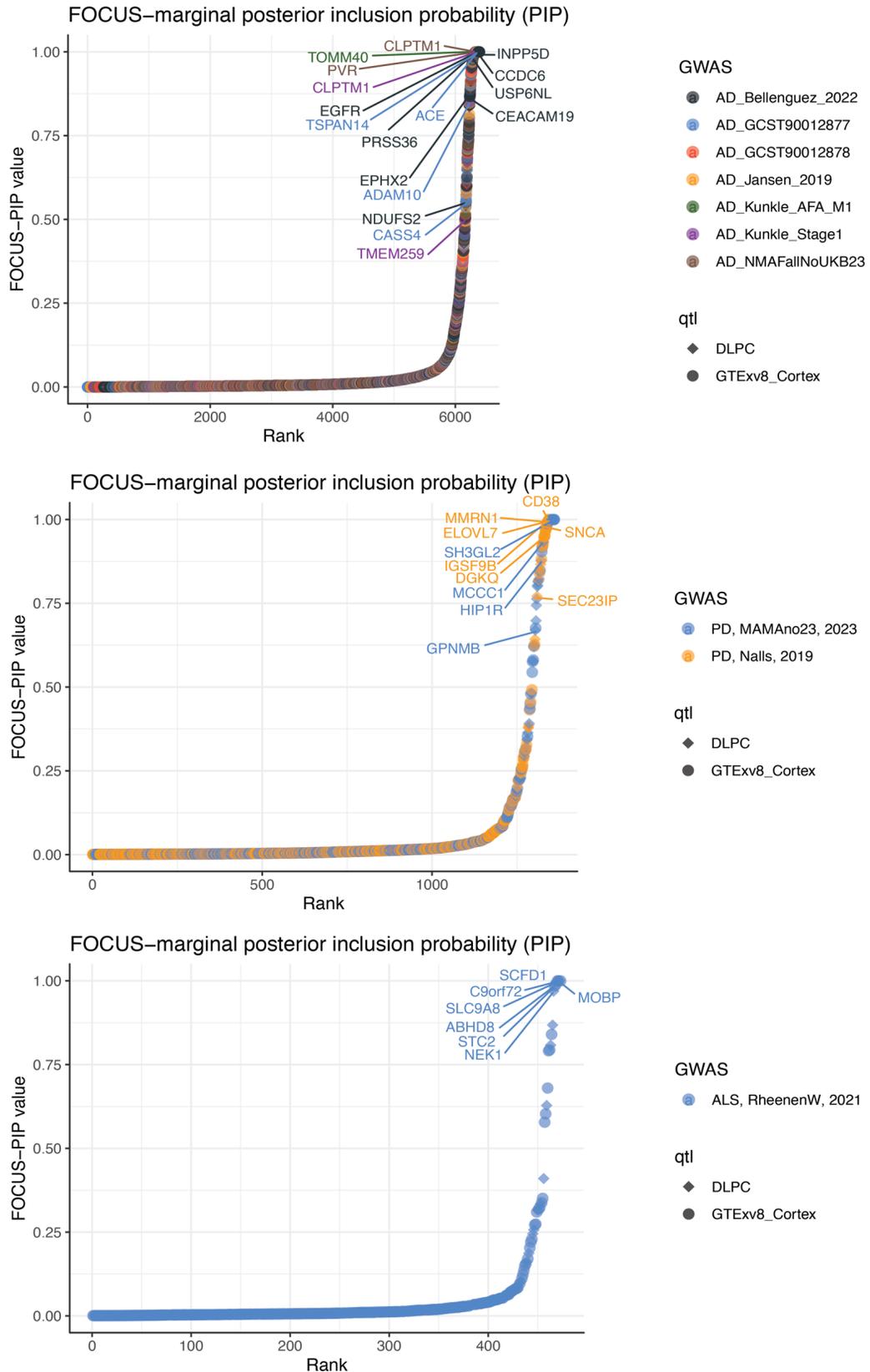
**Supplementary Figure 2. Colocalization of brain region eQTLs with Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) GWAS signals.** Three different shapes represent AD, PD, and ALS GWAS data sources. Twelve colors denote eQTL data sources from different brain regions.

# Supplementary Figure 3



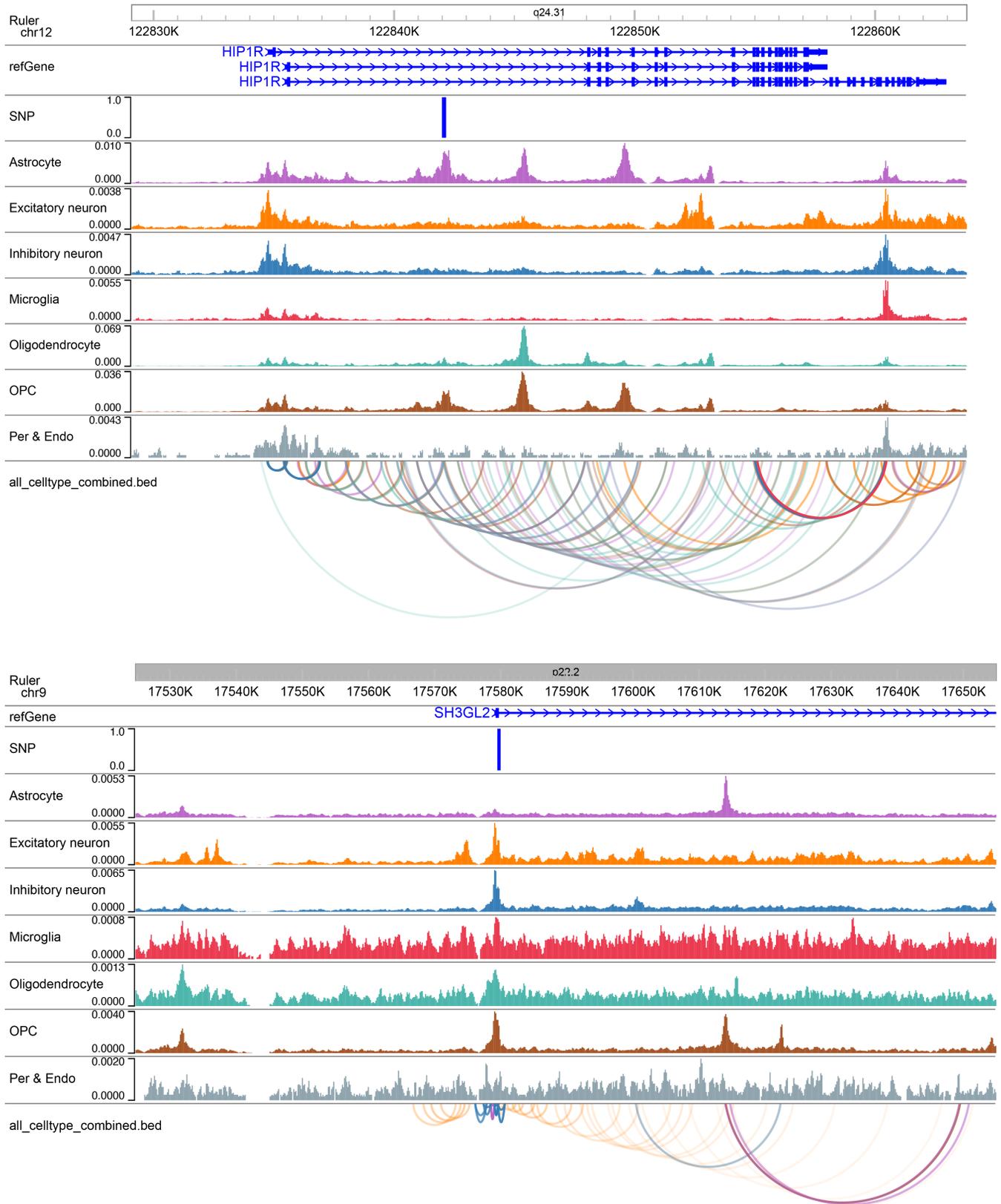
**Supplementary Figure 3. Colocalization of brain cell type specific eQTLs with Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) GWAS signals.** Three different shapes represent AD, PD, and ALS GWAS data sources. Colors denote eQTL data sources from different cell types.

# Supplementary Figure 4



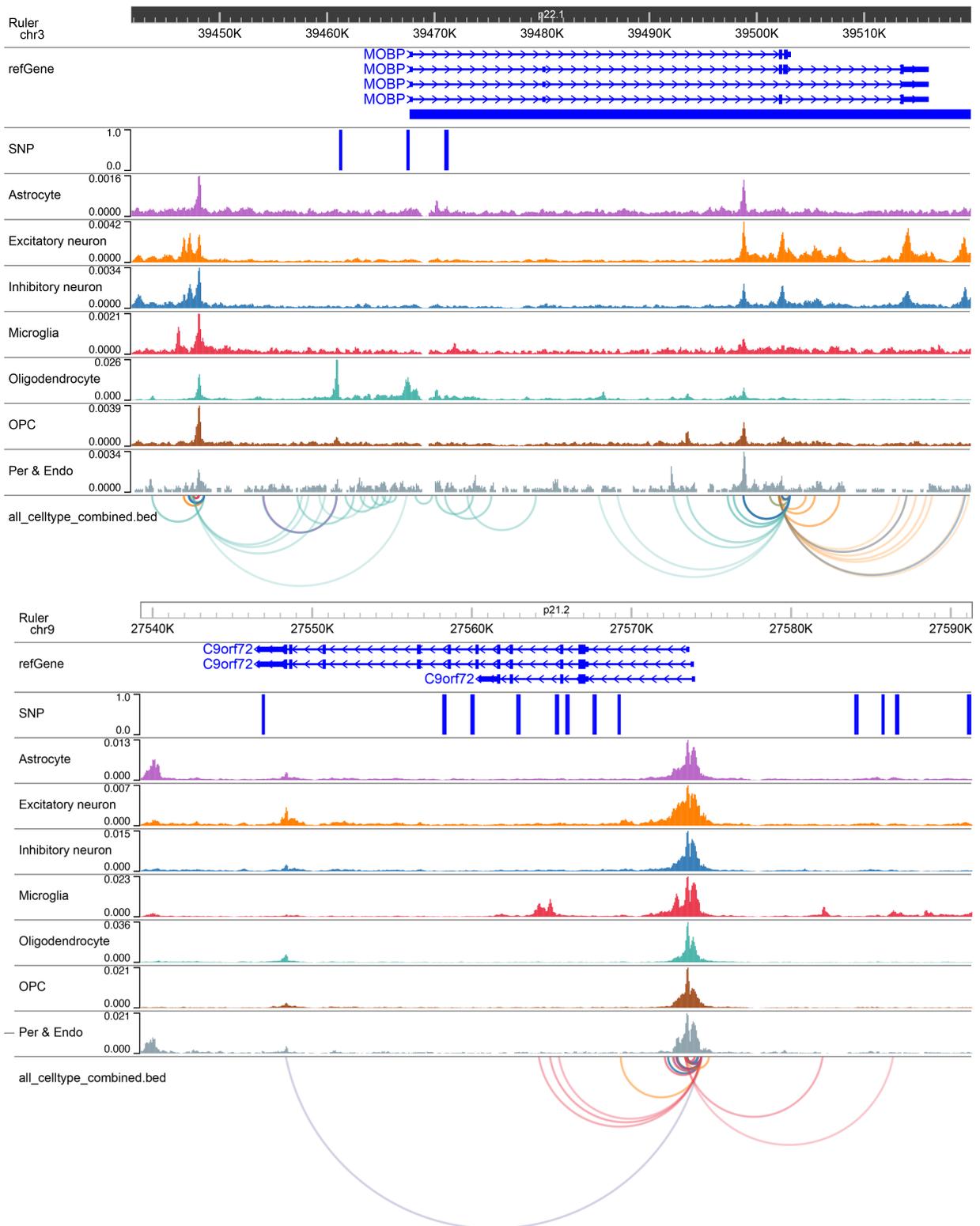
**Supplementary Figure 4. FOCUS fine-mapping analysis for Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).** Colors indicate different GWAS datasets and shapes indicate the QTL data used for analysis.

# Supplementary Figure 5



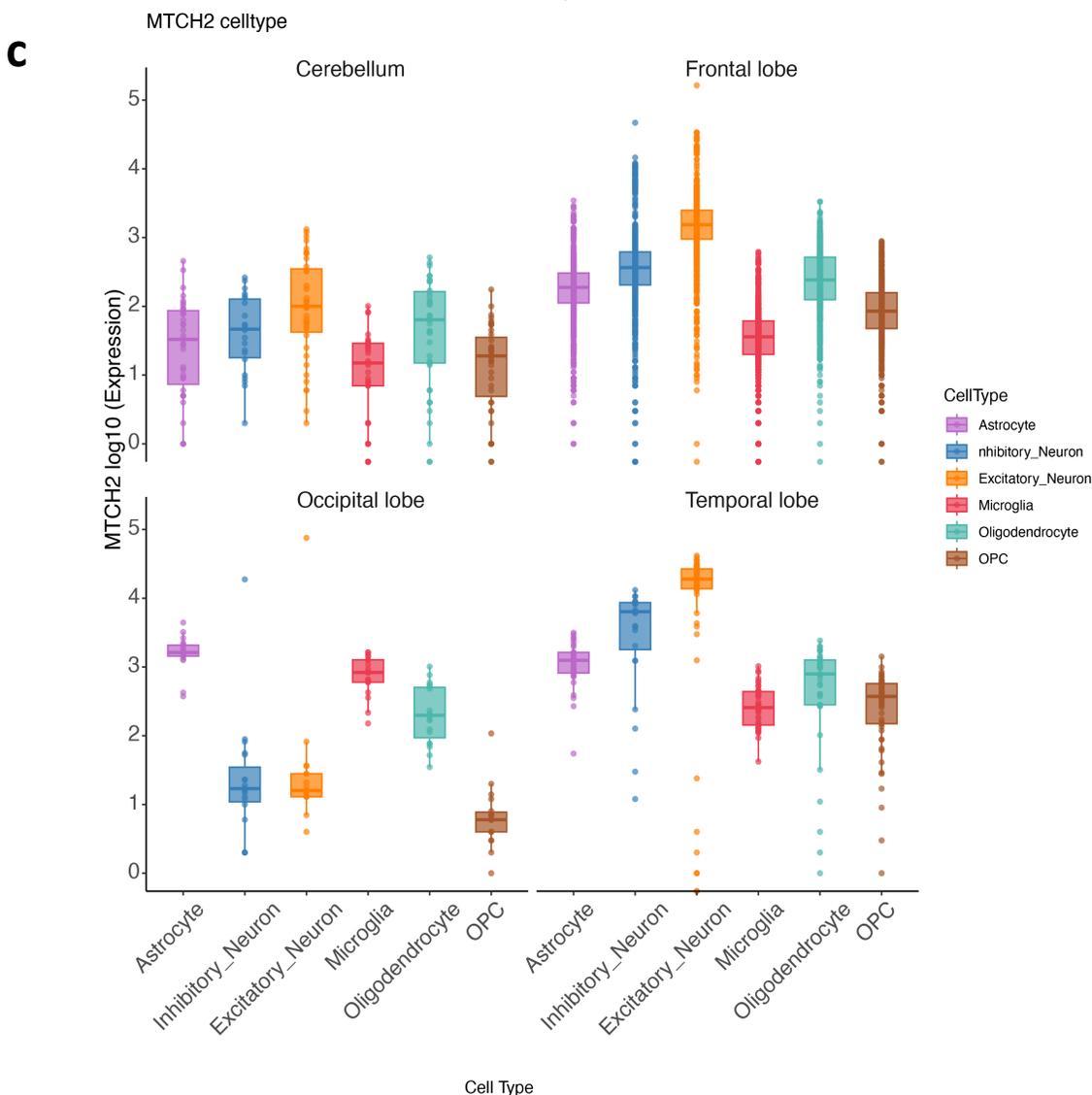
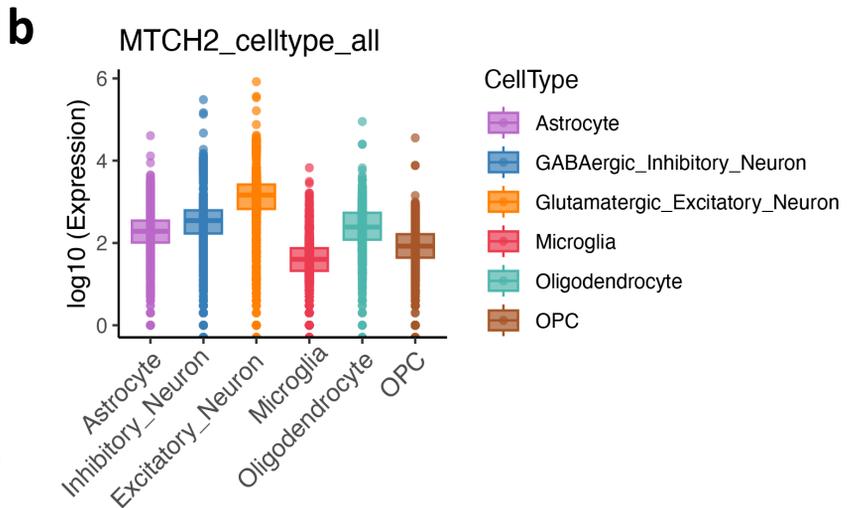
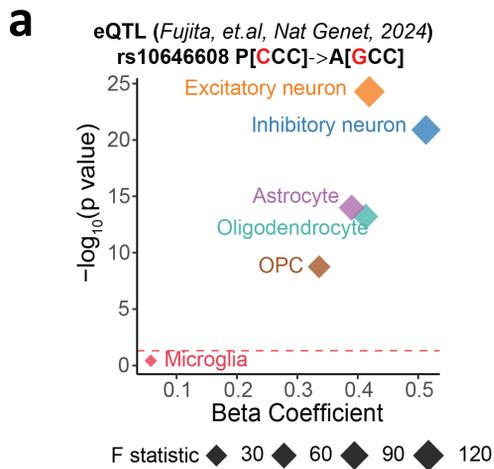
**Supplementary Figure 5. The case studies of SNP-gene pairs validated by peak-to-gene analysis for Parkinson's disease (PD).** a. snATAC-seq and peak-to-gene loop validated SNP-gene association pairs across PD. Different colored arch lines denote cell type specific significant peak-to-gene associations and the colorful peaks indicate chromatin accessibility in snATAC-seq data.

# Supplementary Figure 6



**Supplementary Figure 6. The case studies of SNP-gene pairs validated by peak-to-gene analysis for amyotrophic lateral sclerosis (ALS).** a. snATAC-seq and peak-to-gene loop validated SNP-gene association pairs across ALS. Different colored arch lines denote cell type specific significant peak-to-gene associations, and the colorful peaks indicate chromatin accessibility in snATAC-seq data.

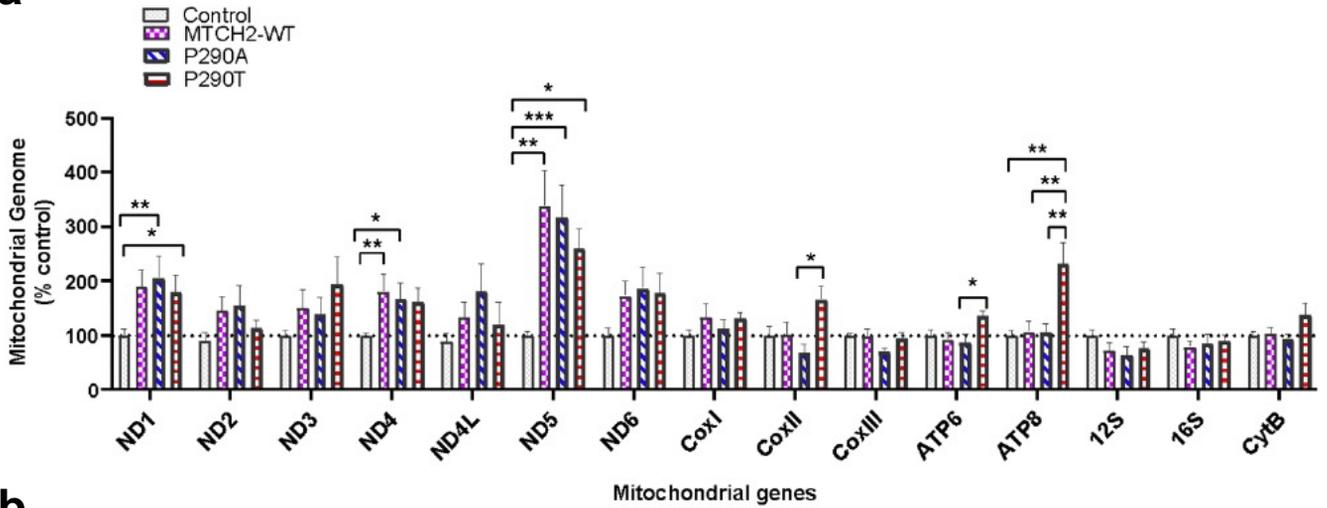
# Supplementary Figure 7



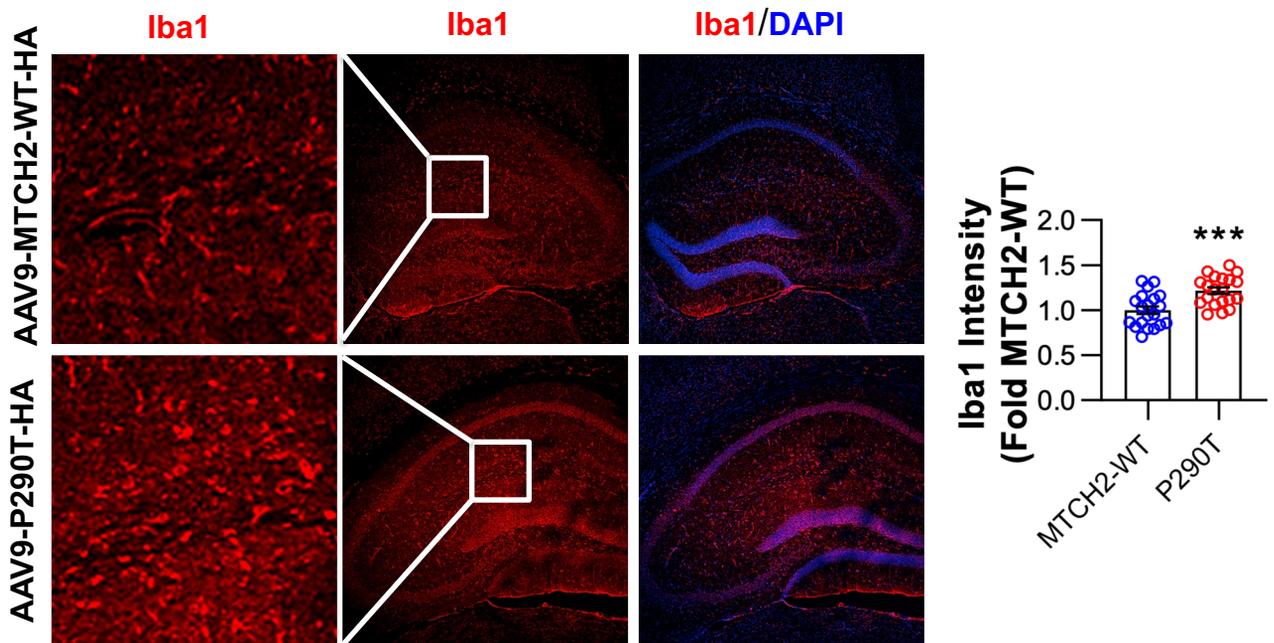
**Supplementary Figure 7. *MTCH2* eQTL data and expression level across different human brain cell types.** **a**, Cell type specific eQTL of *MTCH2* nonsynonymous mutation rs10646608 p.P290A (C>G). OPC: oligodendrocyte precursor cells. **b-c**, *MTCH2* expression levels across cell types (**b**) and brain regions (**c**).

# Supplementary Figure 8

**a**



**b**



**Supplementary Figure 8. *MTCH2* shows strong genetic evidence in vivo in mouse brains by AAV experiments. a**, The mitochondrial genome expression comparing in the groups of MTCH-WT, P290A, P290T and controls. **b**, Representative images of IBA1 in the brains of C57BL6/J mice injected with rAAV9-*MTCH2*<sup>WT</sup>-HA and rAAV9-*MTCH2*<sup>p.P290T</sup>-HA. Quantification of IBA1 intensity (t-test, \*\*\* $P < 0.001$ ,  $n = 4$  mice/group).