**Figure S1. Quality control and Cell type annotations of the PiD and AD snATAC-seq datasets. a**, Vilion plot showing the number of the peak counts in the cell type clusters from the PiD and AD human PFC snATAC-seq dataset. **b**, Vilion plot showing the number of UMI, genes and mitochondrial percentage in the samples from the PiD snRNA-seq dataset. **c**, Integrated Uniform Manifold Approximation and Projection (UMAP) visualizations by diagnosis for snRNA-seq and snATAC-seq data from PiD and AD. **d**, Uniform Manifold Approximation and Projection (UMAP) visualizations for clusters of snRNA-seq data from PiD. **e**, Heatmap of canonical cell-type markers for snRNA-seq data from PiD. **f**, Coverage plots for canonical cell-type markers in AD dataset: GFAP (chr17:44905000-44916000) for astrocytes, SYNPR (chr3:63278010-63278510) for neurons, SLC17A6 (chr11:22338004-22345067) for excitatory neurons, GAD2 (chr10:26214210-26241766) for inhibitory neurons, CSF1R (chr5:150056500-150087500) for microglia, MOBP (chr3:39467000-39488000) for oligodendrocytes, PDGFRA (chr4:54224871-54300000) for Pericytes and Endothelial Cells in PiD dataset. The grey bar within each box highlights the promoter regions.
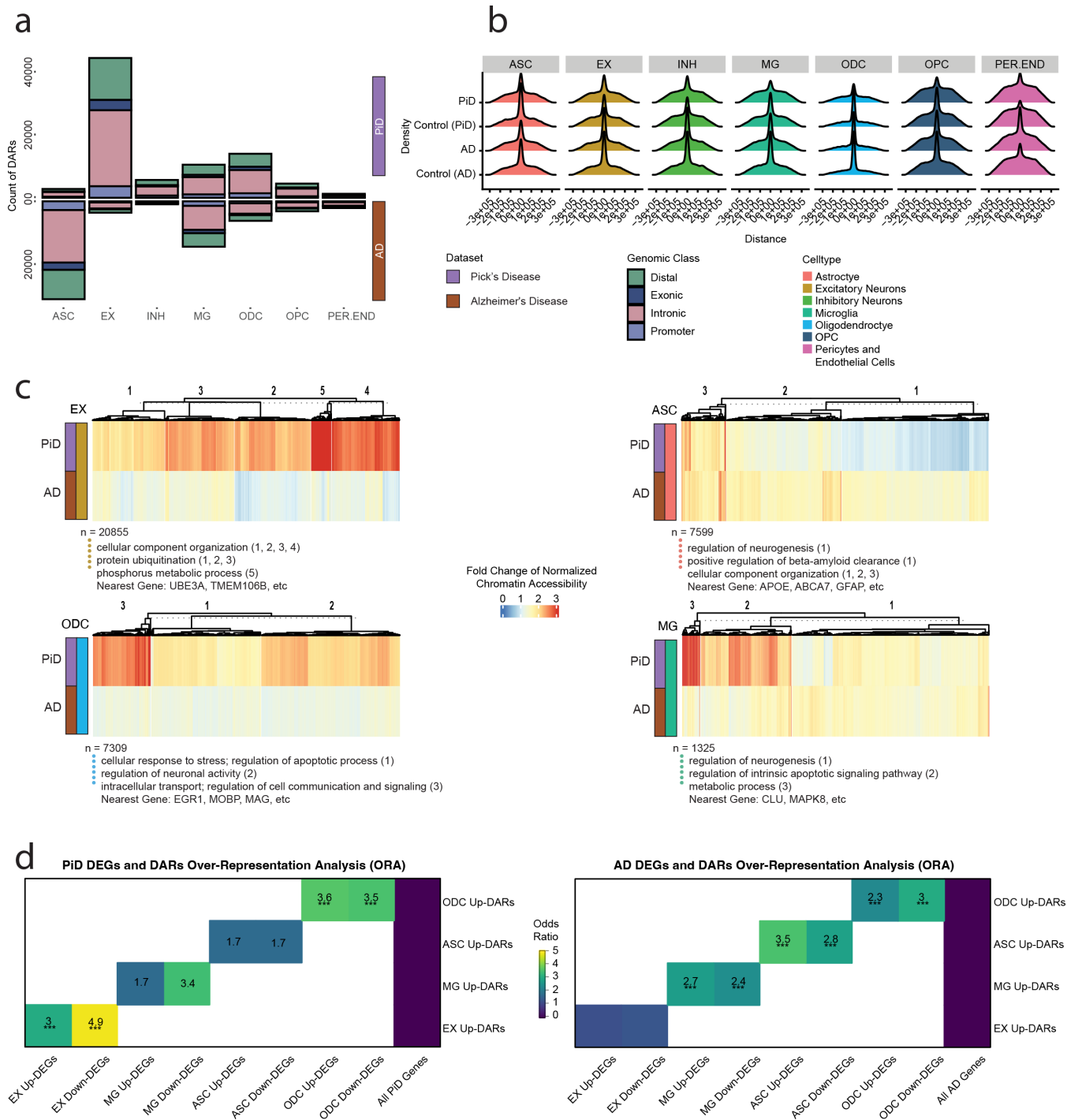
Figure S2. Different accessible CREs by cell types. a, Genomic type classification of differential open accessible regions group by cell types (P-value < 0.05) between PiD. AD with their respective controls. **b**, Ridgeline plot showing the distance of imputed enhancers from the promoters. **c**, Heatmaps of fold changes (Disease vs. Control) on normalized chromatin accessibility of differential accessible intronic in excitatory neurons, astrocytes, microglia and oligodendrocytes (FDR adjusted P-value < 0.05 and abs(log2FC) > 0.5), gene ontology acquired from GREAT and examples of promoters and distal regions' cis-regulatory linked gene as in the panel of Figure **??**e. **d**, Over-representation analysis (ORA) of DEGs (snRNA-seq) and DARs (snATAC-seq) from PiD and AD.
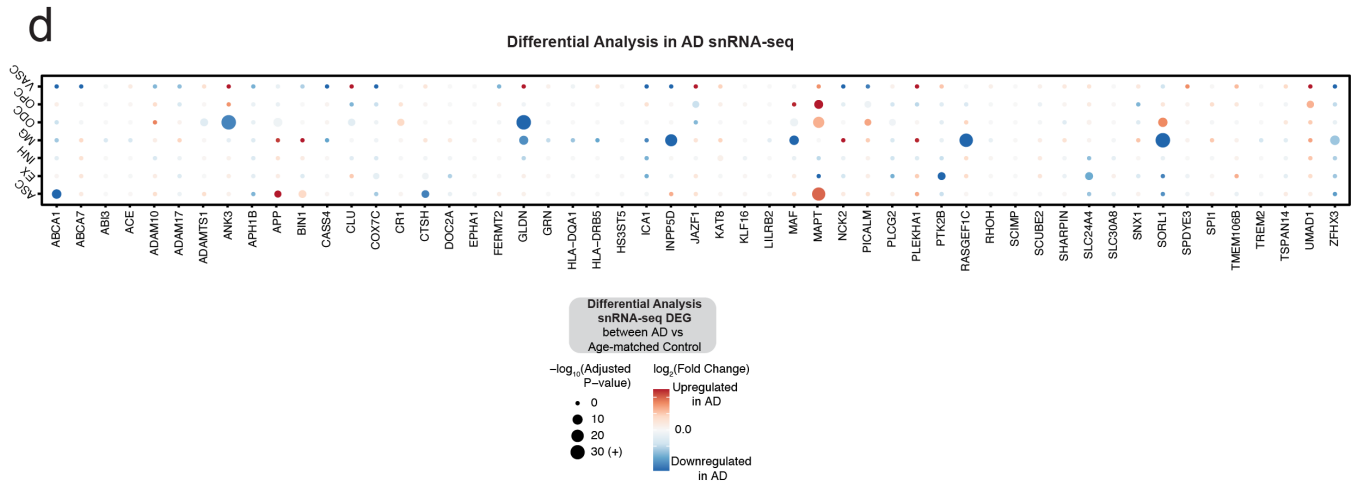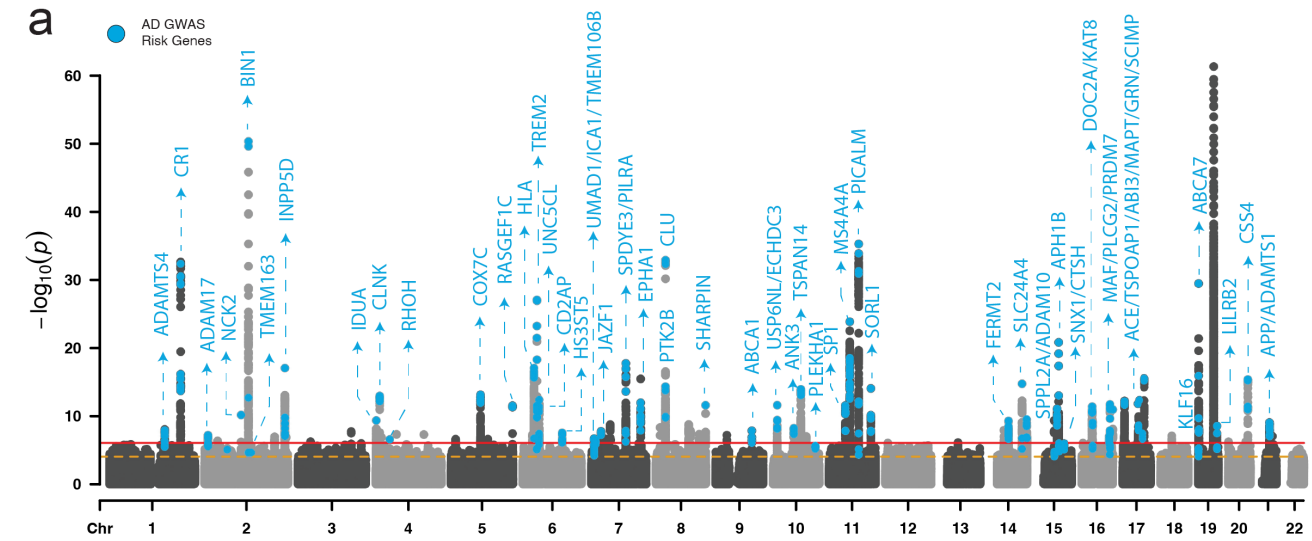
Figure S3. Characterization of the genetic landscape of Alzheimer's disease and Frontotemporal dementia. a, Manhattan plot of Alzheimer's disease[?] . **b**, The dotplot on the far right shows the snRNA-seq differentially expressed GWAS gene in each cell type between AD and age-matched control samples.
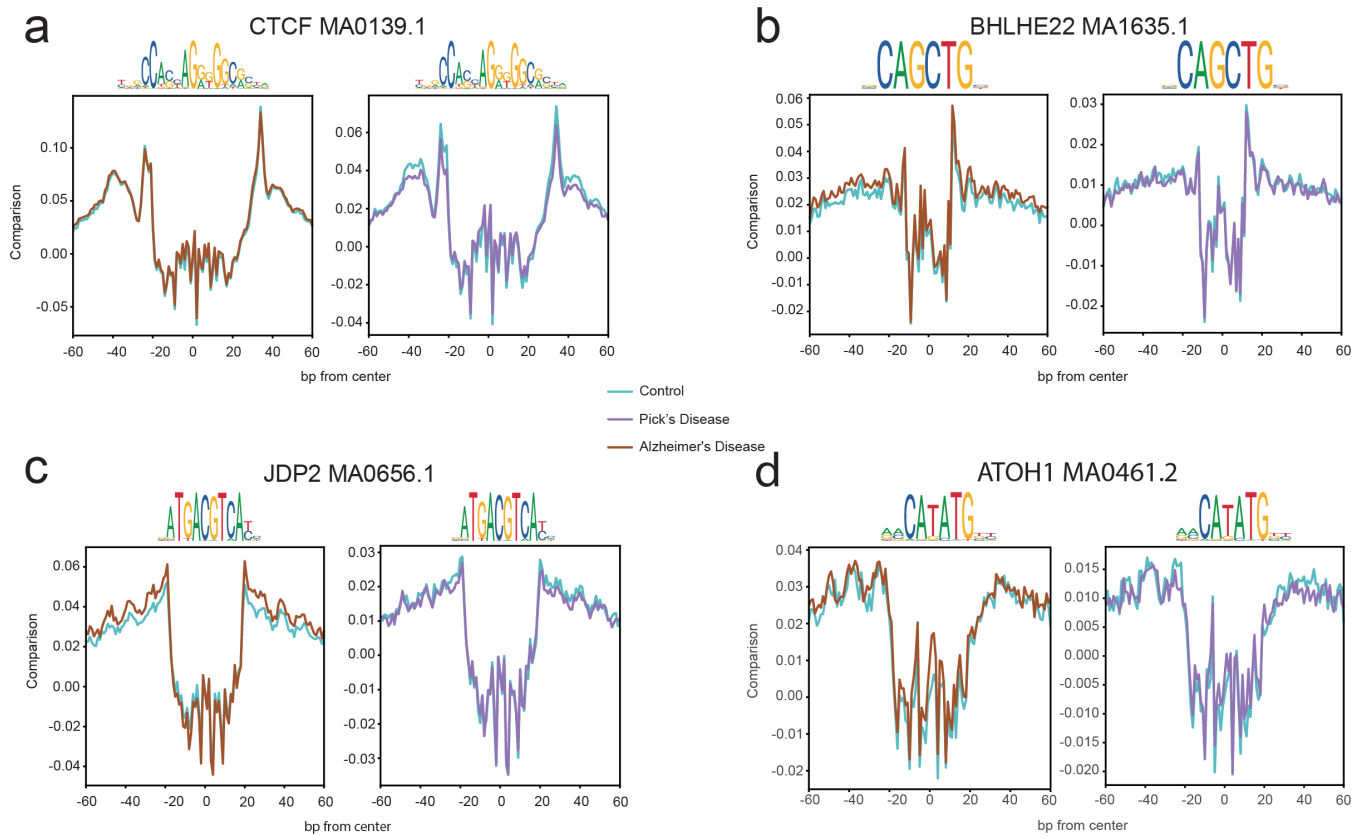
Figure S4. Aggregated footprints of TFs in excitatory neurons. a, Aggregated TF footprints of CTCF (MA0139.1) in AD and PiD. **b**, Aggregated TF footprints of BHLHE22 (MA1635.1) in AD and PiD. **c** Aggregated TF footprints of JDP2 (MA0656.1) in AD and PiD. **d** Aggregated TF footprints of ATOH1 (MA0461.1) in AD and PiD.
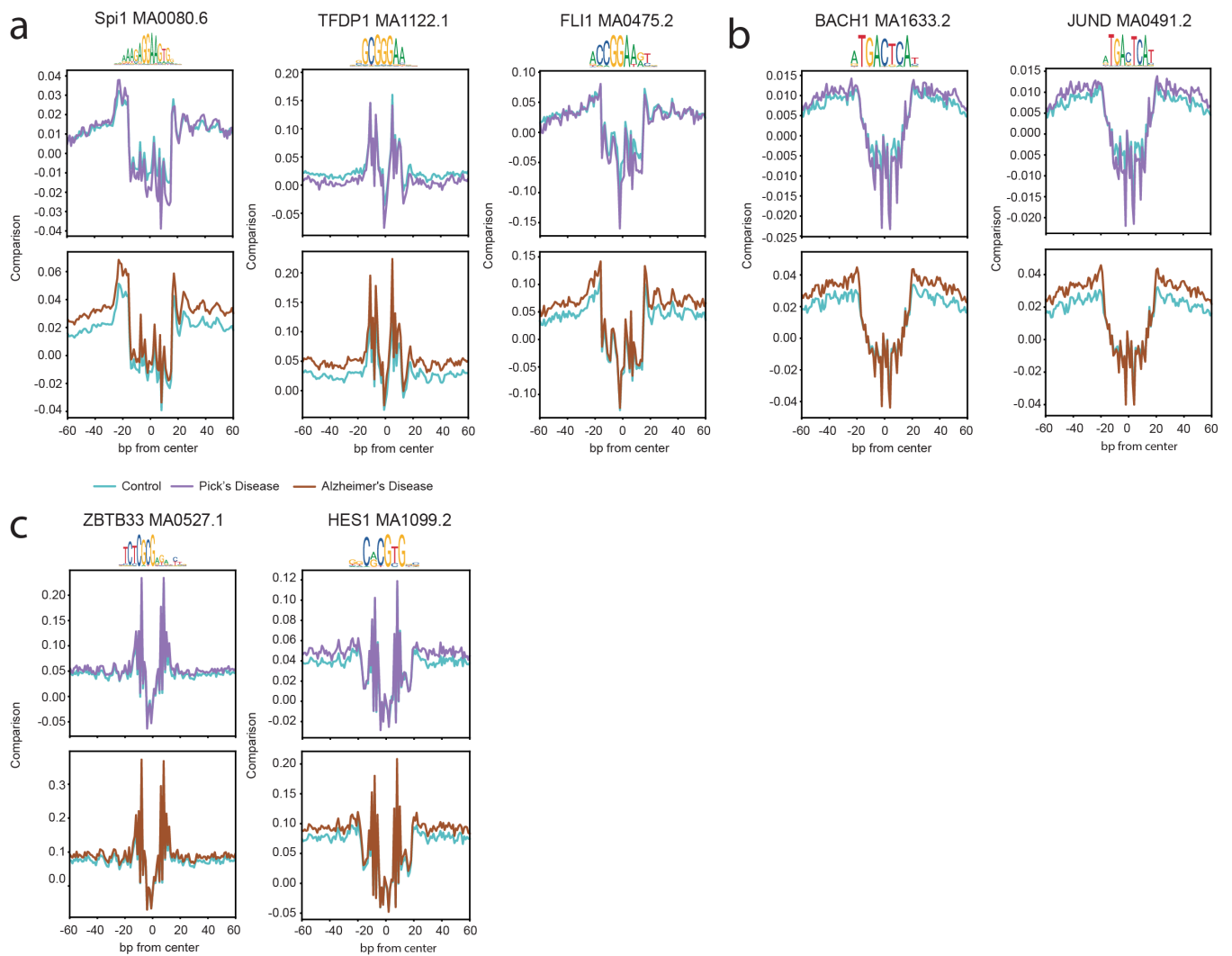
Figure S5. Aggregated footprints of TFs in MG, AST, and ODC. a, Aggregated TF footprints of Spi1 (MA0080.6), TFDP1 (MA1122.1) and FLI1 (MA0475.2) in PiD and AD. **b**, Aggregated TF footprints of BACH1 (MA1633.2) and JUND (MA0491.2) in PiD and AD. **c** Aggregated TF footprints of ZBTB33 (MA0527.1) and HES1 (MA1099.2) in PiD and AD.