Supplementary Figure

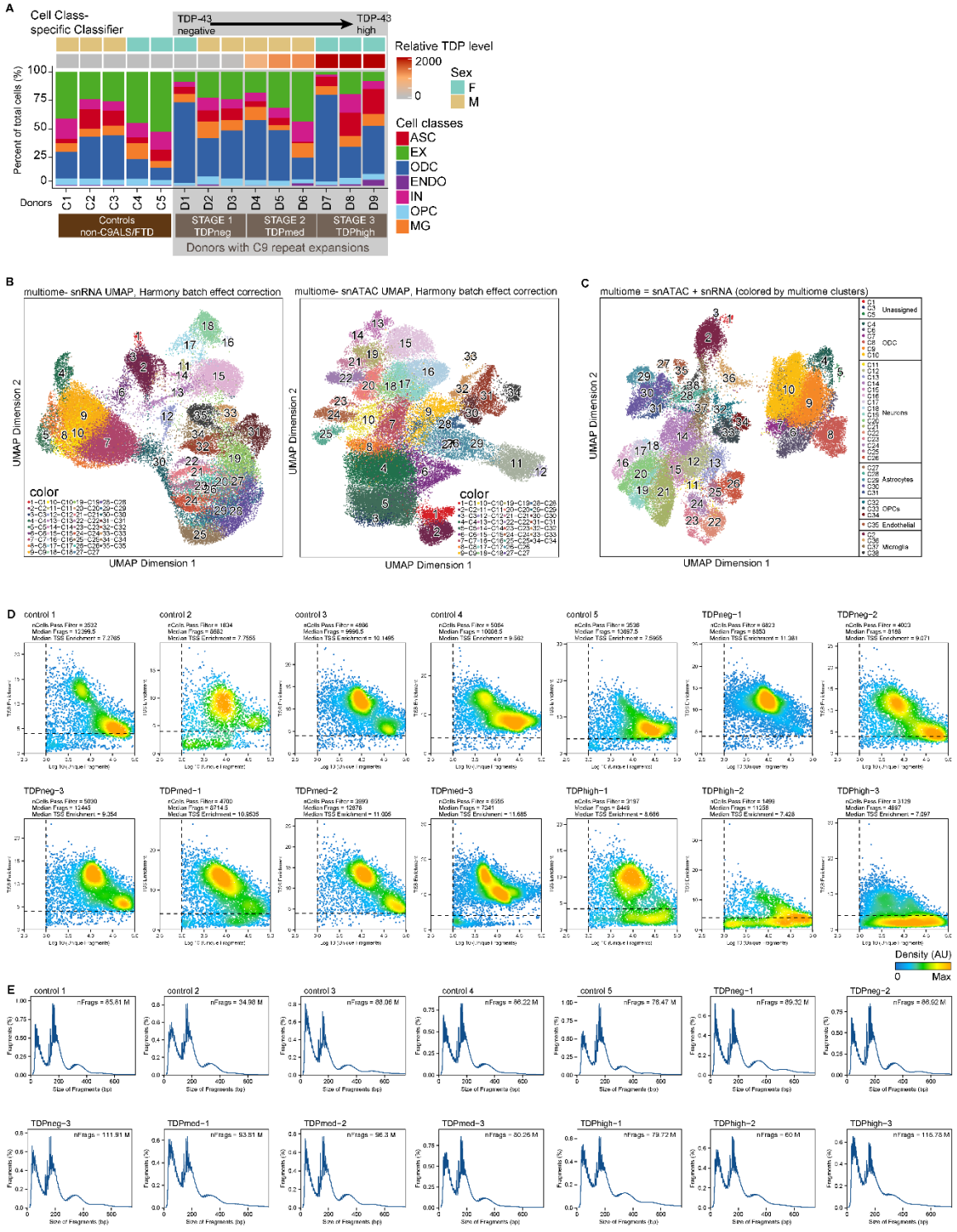

Fig. S1. Confirmation of performance using paired snATAC-seq and snRNA-seq data from the same cell of all donor samples.

(A) *C9orf72* ALS/FTD cases were staged by pTDP-43 abundance and the proportions of major cell classes are shown. (B) UMAP visualizations of iterative LSI of snRNA-seq (left) and iterative LSI of snATAC-seq (right). (C) Iterative LSI of combined snATAC-seq and snRNA-seq. Cells are colored based on clusters identified in each iterative LSI. (D) Quality control metrics for the snATAC-seq dataset showing the TSS enrichment score vs unique nuclear fragments per cell. (E) Fragment size distribution for cells in each sample passing ArchR QC thresholds.

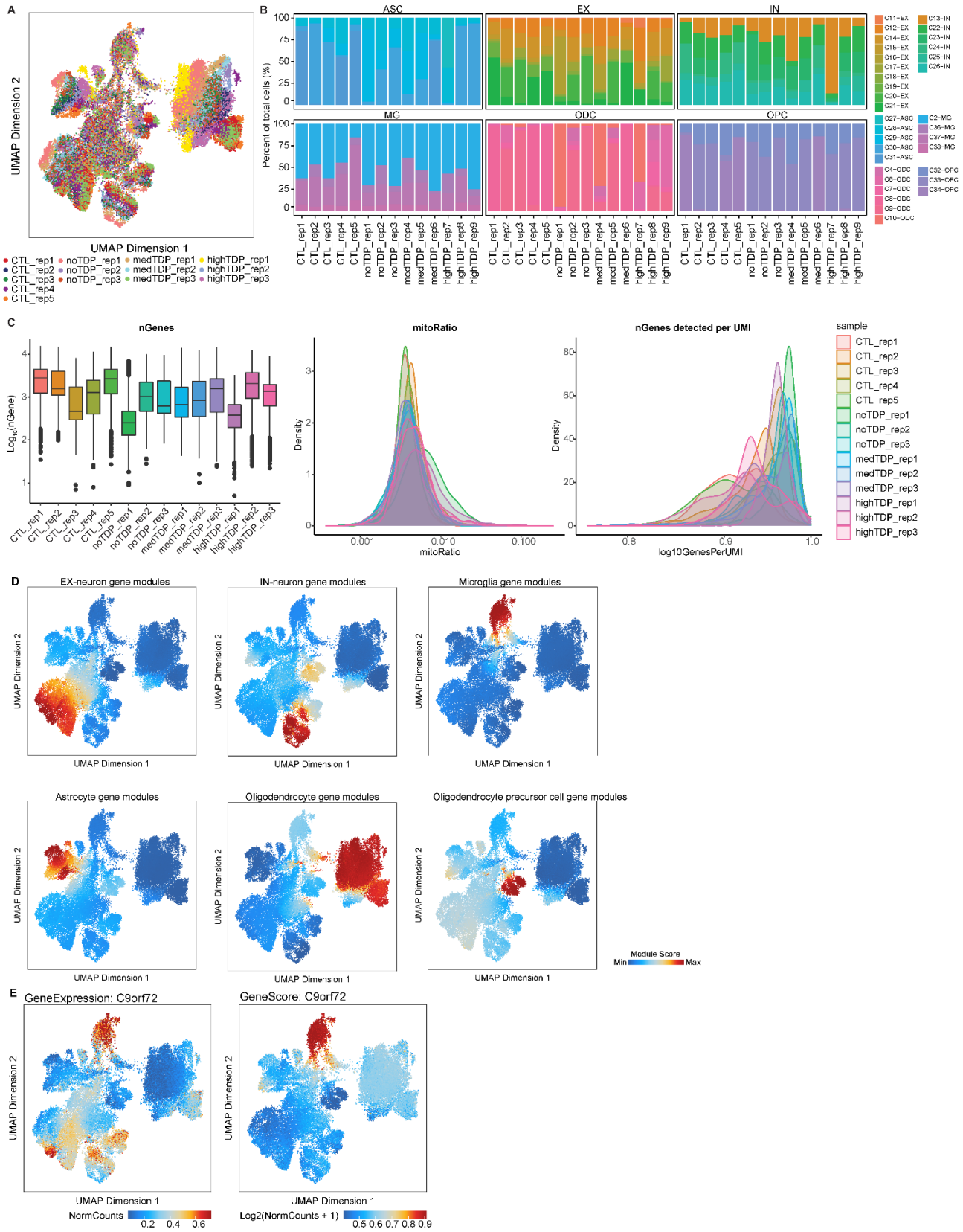

Fig. S2. Quality control and gene module and gene activity scores.
(A) snATAC-seq and snRNA-seq integrated UMAP colored by samples analyzed. (B) Proportion of all clusters per sample. (C) Quality control of snRNA-seq. (D) Gene module scores of major cell types. (E) Gene activity score and gene expression of the *C9orf72* gene.

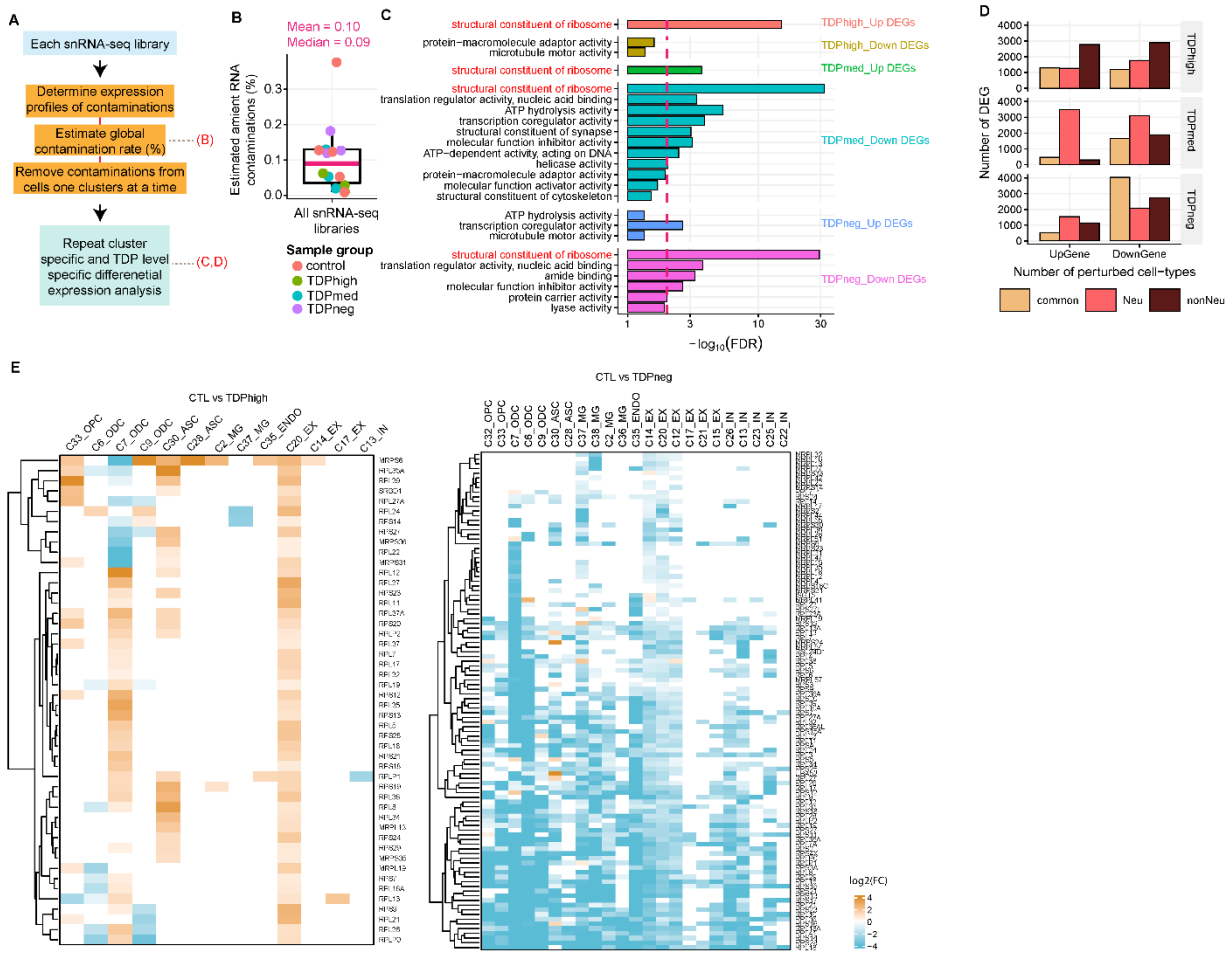

Fig. S3. Differential gene expression comparisons after removal of ambient RNA contamination. (A) Schematic representation of ambient RNA analysis. (B) Average ambient RNA contamination in each snRNA-seq library. All libraries have less than 20% estimated global ambient RNA contamination except for control library c4. (C) GO enrichment analysis of DEGs common to neuronal and non-neuronal cells performed independently for each pTDP-43 group. (D) Number of DEGs for each pTDP-43 donor group common among neuronal and non-neuronal cells. (E) DEGs encoding for structural constituents of the ribosome (Fig. S3C) for each cell cluster. Left: fold change in the TDPhigh donor group vs control; Right: fold change in the TPDneg donor group vs control.

Supplementary Tables

Table S1. Sample metadata.

Table S2. Cellranger-arc quality control data for each sample, including both the snATAC-seq and snRNA-seq libraries.

Table S3. List of marker genes for each cell cluster.

Table S4. List of differentially expressed genes and differential chromatin accessible regions and gene ontology analysis of neuronal and nonneuronal common differentially expressed genes.

Table S5. Analysis of differentially expressed genes after removal of ambient RNA using SoupX.

Table S6. List of differentially expressed genes enriched for mitochondria-related ontology terms

Table S7. List of WGCNA module eigengenes found in excitatory and inhibitory neuron clusters.