Description of Additional Supplementary Files

Title: Supplementary Data 1

Description: Marker genes for CNS cell-type annotation and confirmation of choroid plexus epithelial cell (CPC) identity. Left: top marker genes for each of the twelve annotated CNS populations (CPCs, endothelial cells, microglia, oligodendrocytes, neurons, ependymal cells, macrophages, astrocytes, olfactory ensheathing glia, pericytes, arachnoid barrier cells, and oligodendrocyte precursor cells), identified by comparing each cluster against all remaining cells (Seurat FindAllMarkers; two-sided Wilcoxon rank-sum test, Bonferroni-adjusted). Shown are the average $\log_2$ fold change, Bonferroni-adjusted P value, and the percentage of cells expressing each gene within the cluster and among all other cells. Right: a curated panel of canonical CPC markers used to classify the two subclusters obtained by re-clustering CPCs at higher resolution; expression across these markers (same test) confirmed both subclusters as CPCs. Panel compiled from Ximerakis et al. (Nat. Neurosci. 2019), Dani et al. (Cell 2021), and PanglaoDB (Franzén et al., Database 2019).

Title: Supplementary Data 2

Description: Differential gene expression (DGE) between mKate2$^+$ and mKate2$^-$ cells across the twelve CNS cell populations (red, upregulated; blue, downregulated).

Title: Supplementary Data 3

Description: Functional annotation and pathway enrichment of commonly up-regulated genes (related to Fig. 4G). Input genes were those with a common expression score (CES) ≥ 6 across the twelve CNS cell populations — i.e., consistently up-regulated between mKate2$^+$ and mKate2$^-$ cells (Supplementary Data 2) — analysed by enrichment network analysis in Metascape. Annotation: each input gene with its Gene ID, symbol, description, associated Gene Ontology biological processes, and membership (1 = member, 0 = non-member) in the top enriched terms. Enrichment: enriched ontology terms and pathways (GO Biological Process, KEGG, Reactome) grouped into clusters of related terms, showing the enrichment P value (LogP, $\log_{10}$), Benjamini–Hochberg-corrected q value (Log(q-value), $\log_{10}$), member genes, and gene ratio (InTerm_InList). Term enrichment was assessed by the one-sided cumulative hypergeometric test with Benjamini–Hochberg correction for multiple comparisons.

Title: Supplementary Data 4

Description: Functional annotation and pathway enrichment of commonly down-regulated genes (related to Supplementary Fig. 9). Input genes were those with a common expression score (CES) < −6 across the twelve CNS cell populations — i.e., consistently down-regulated between mKate2$^+$ and mKate2$^-$ cells (Supplementary Data 2) — analyzed by enrichment network analysis in Metascape. Summary worksheet: the top non-redundant enriched terms, with category, description, gene count, percentage of input genes, enrichment P value (Log10(P)), and Benjamini–Hochberg-corrected q value (Log10(q)). Annotation worksheet: each input gene with its Gene ID, symbol, description, associated Gene Ontology biological processes, and membership (1 = member, 0 = non-member) in the top enriched terms. Enrichment worksheet: all enriched ontology terms and pathways (GO Biological Process, KEGG, Reactome, WikiPathways) grouped into clusters of related terms, showing the enrichment P value (LogP, $\log_{10}$), Benjamini–Hochberg-corrected q value (Log(q-value), $\log_{10}$), member genes, and gene ratio (InTerm_InList). Term enrichment was assessed by the one-sided cumulative hypergeometric test with Benjamini–Hochberg correction for multiple comparisons.

Title: Supplementary Data 5

Description: Normalized enrichment scores (NES) for all significantly altered Gene Ontology Biological Process (GOBP) pathways across the twelve CNS cell types.

Title: Supplementary Data 6

Description: Normalized enrichment scores (NES) for all significantly altered GOBP pathways in astrocytes, neurons, microglia, and oligodendrocytes.

Title: Supplementary Data 7

Description: Curated list of 52 marker genes previously associated with cardiac phenotypes in Friedreich's ataxia (FA) murine and cellular models. Genes are grouped by functional category — heart failure, hypertrophic cardiomyopathy, iron metabolism, β-oxidation and glycolysis, fibrosis, electron transport and TCA cycle, and Nrf2 targets — and listed with their mouse gene symbol and description. For each gene, checkmarks indicate the prior study or studies (Salinas et al., 2024; Sayles et al., 2023; Perdomini et al., 2014; Li et al., 2019; Cotticelli et al., 2023) in which the gene was reported as dysregulated in an FA cardiac model. This gene set forms the basis for the cardiac-phenotype expression analysis shown in Fig. 7I and Supplementary Fig. 17.

Title: Supplementary Data 8

Description: Differentially expressed genes in DP+FA versus FA+FA hearts (bulk RNA-sequencing; related to Fig. 7). Genes differentially expressed between DP+FA (n = 3) and FA+FA (n = 3) mouse hearts, identified from raw read counts using DESeq2 (v1.40.2). For each gene, the $\log_2$ fold change (DP+FA relative to FA+FA) and adjusted P value are listed, ranked by $\log_2$ fold change. Differential expression was assessed by the two-sided Wald test based on a negative binomial generalized linear model (DESeq2); P values were adjusted for multiple comparisons across genes by the Benjamini–Hochberg false-discovery-rate procedure, and genes with adjusted $P < 0.05$ were considered significant.

Title: Supplementary Data 9

Description: Gene set enrichment analysis of DP+FA versus FA+FA hearts (bulk RNA-sequencing; related to Fig. 7J). Gene set enrichment analysis of the DP+FA versus FA+FA bulk RNA-sequencing comparison (n = 3 per group), performed with fGSEA (v1.26) against all Gene Ontology Biological Process gene sets (MSigDB, msigdbr v7.5.1) on genes ranked by differential expression. Sheet 1 (complete): results for all tested gene sets. Sheet 2 (significant): the significantly enriched gene sets, ranked by normalized enrichment score. For each gene set, the enrichment P value (pval), Benjamini–Hochberg-adjusted P value (padj), P-value estimation error (log2err), enrichment score (ES), normalized enrichment score (NES), gene-set size, and leading-edge genes are shown. Enrichment P values are two-sided — a positive NES indicates enrichment among genes up-regulated in DP+FA and a negative NES among down-regulated genes — and were adjusted for multiple comparisons across gene sets by the Benjamini–Hochberg false-discovery-rate procedure.