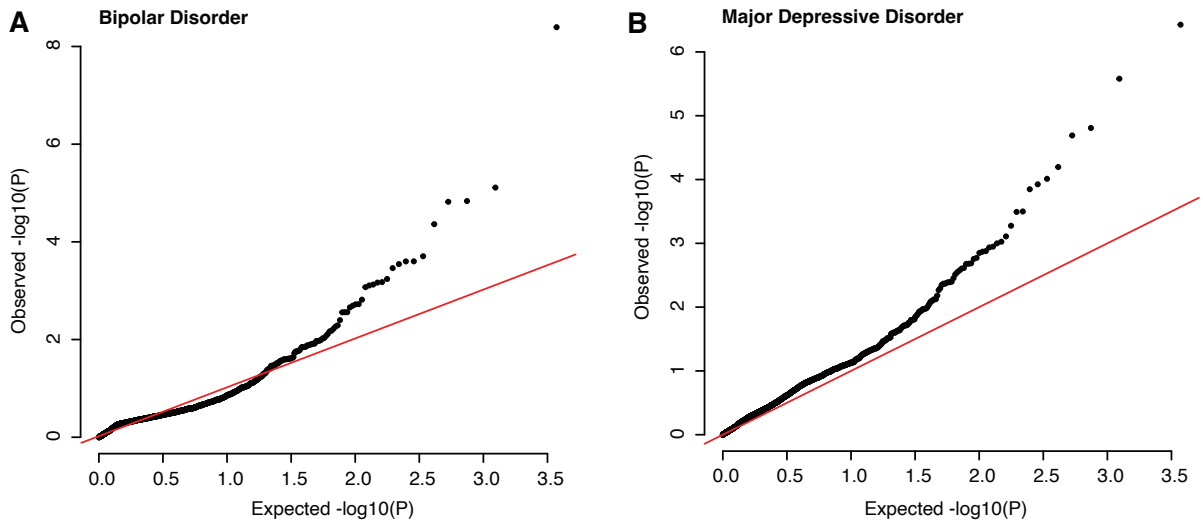

Figure S1. Quantile-quantile plots for exome-wide association studies in the OOA population. A. Bipolar disorder cases vs. controls. **B.** Major depressive disorder cases vs. controls.

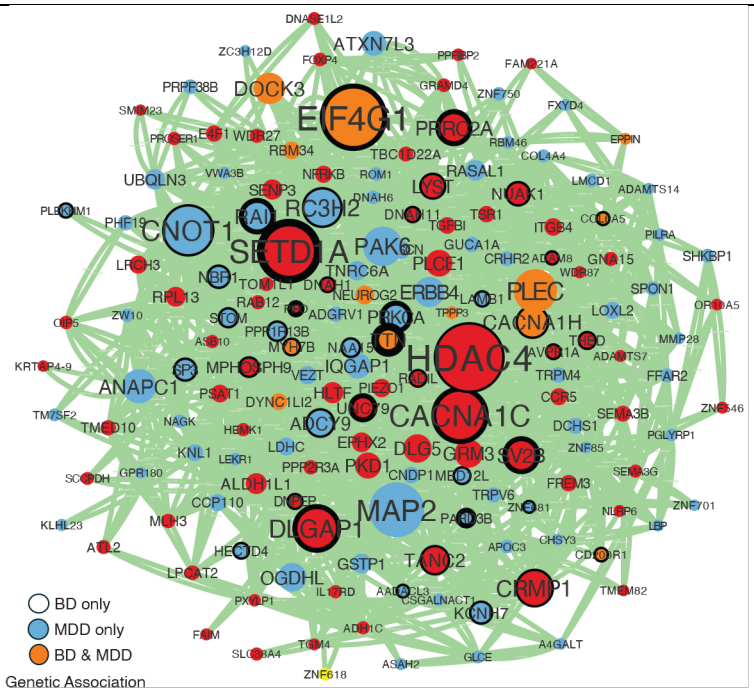

Figure S2. Variant prioritization by network analysis and prior evidence. Node and label size correspond to centrality in a gene interaction network centered on targets of FMRP and their protein-protein interactions from the STRING database. Node border thickness corresponds to the number of prior rare variant studies implicating each gene. Node color corresponds to the diagnoses associated each gene was associated with in the OOA sample.

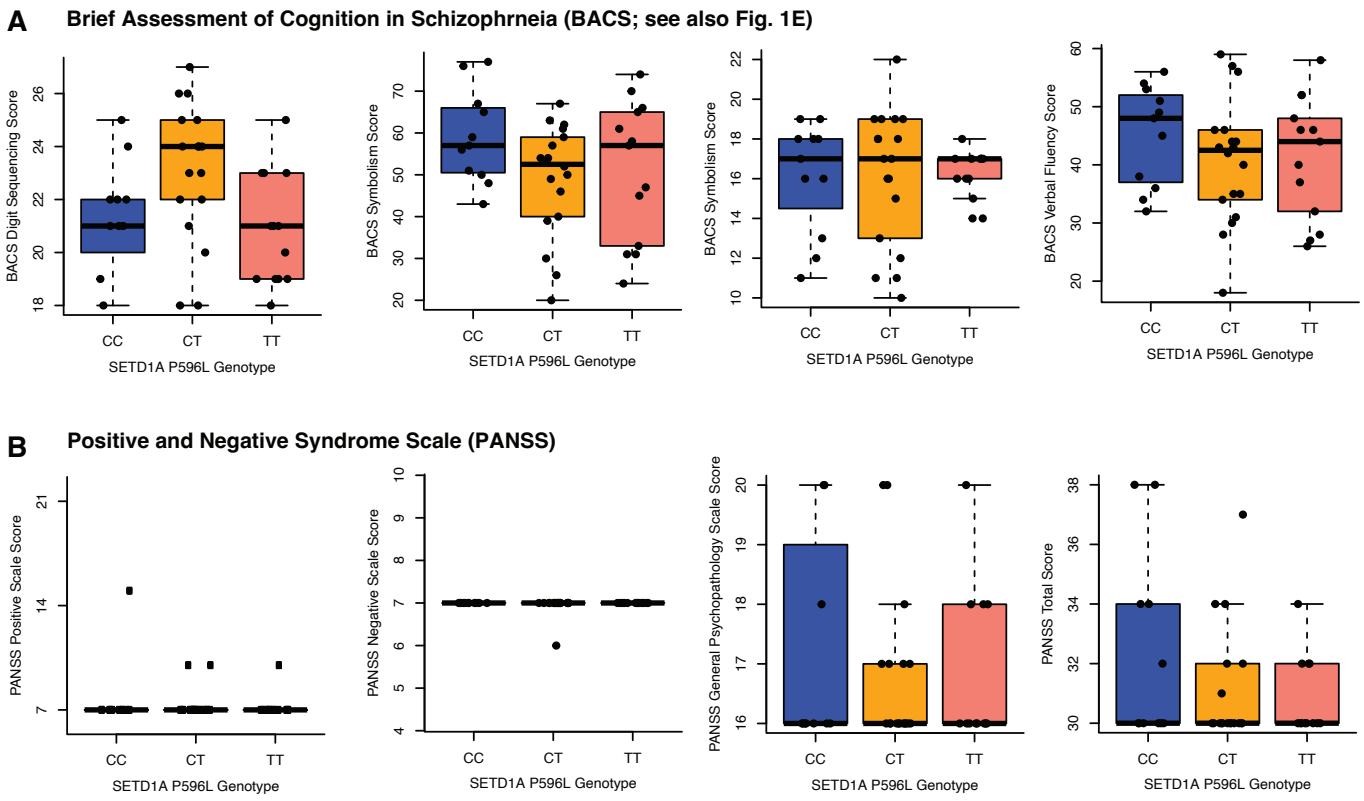

Figure S3. No effect of SETD1A P596L on certain cognitive tasks or on schizophrenia symptoms. A. Subtests of the Brief Assessment of Cognition in Schizophrenia not shown in Fig. 1E. **B.** Positive and Negative Syndrome Scale (PANSS).

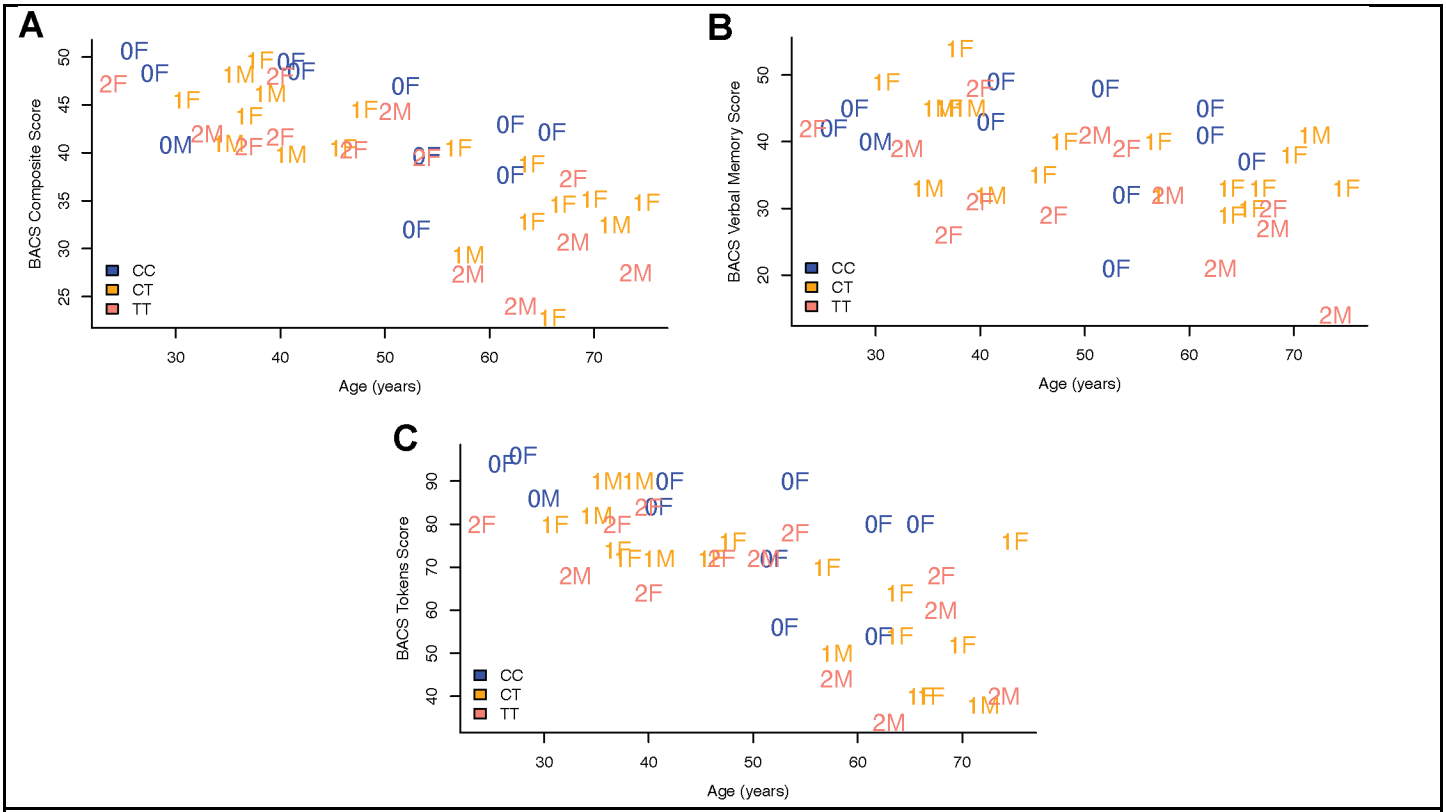

Figure S4. Effects of SETD1A P596L genotype, age, and sex on cognitive tasks. For all three of the Brief Assessment of Cognition in Schizophrenia (BACS) subtests with significant effects of SETD1A P596L genotype, there were also significant effects of age ($P < 0.05$), but effects of gender and genotype x age interactions were not significant. The carriers with the lowest scores were >60-years-old. **A.** Composite Score. **B.** Verbal Memory Score. **C.** Tokens Score. Each point is labeled by the participant's gender and the number of copies of the SETD1A P596L alternate (T) allele.

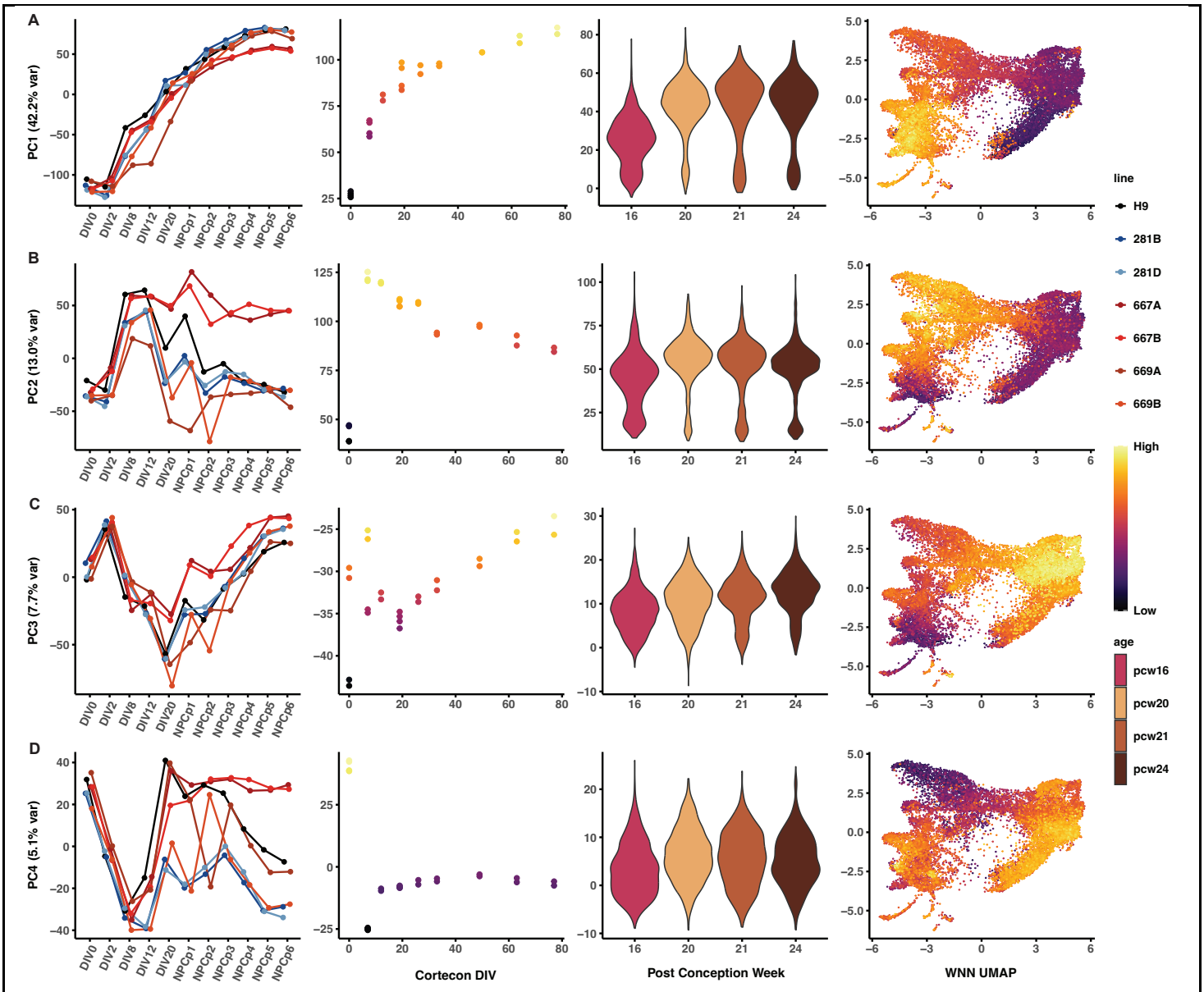

Figure S5. Bulk-defined principal components capture conserved neurodevelopmental programs. A–D. Rows correspond to bulk-computed PCs PC1–PC4. **Left column:** bulk PC scores across neural induction and subsequent NPC passages for each iPSC line. **Second column:** projected PC scores on Cortecon samples. **Third column:** projected PC scores on *in vivo* development samples. **Right column:** projected PC scores mapped onto the scMultiome UMAP. Projected samples and cells colored from low to high projection score.

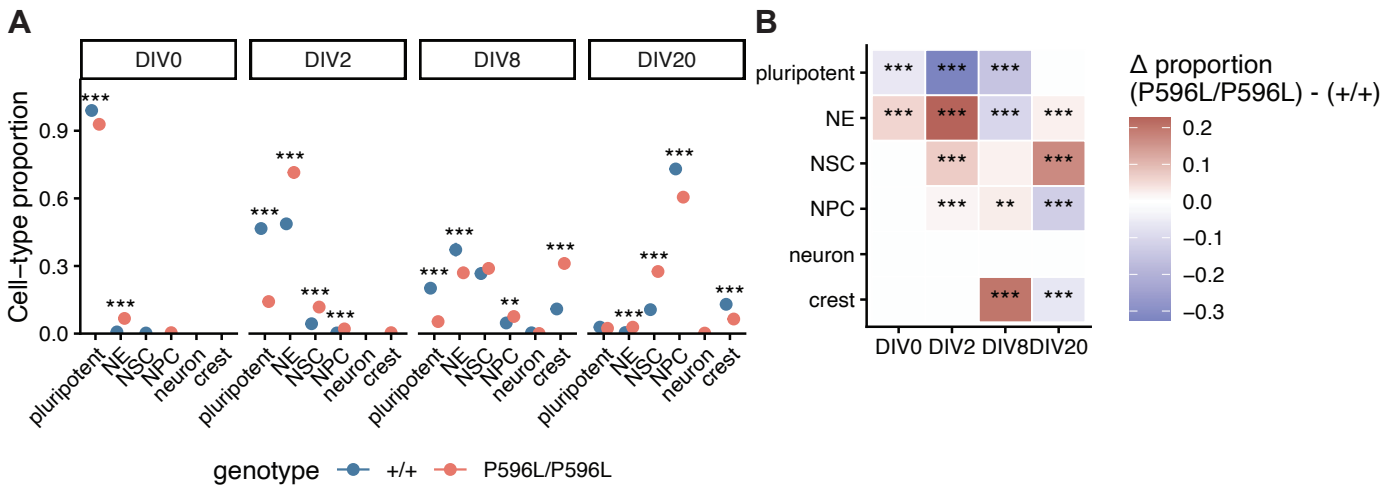

Figure S6. Highest discrepancy in cell type proportions arise at DIV2. A. Genotype-specific cell-type proportions at each DIV profiled (*P<0.05; **P<0.005; ***P<0.0001). **B.** Effect size of differential abundance of cell types across each DIV.

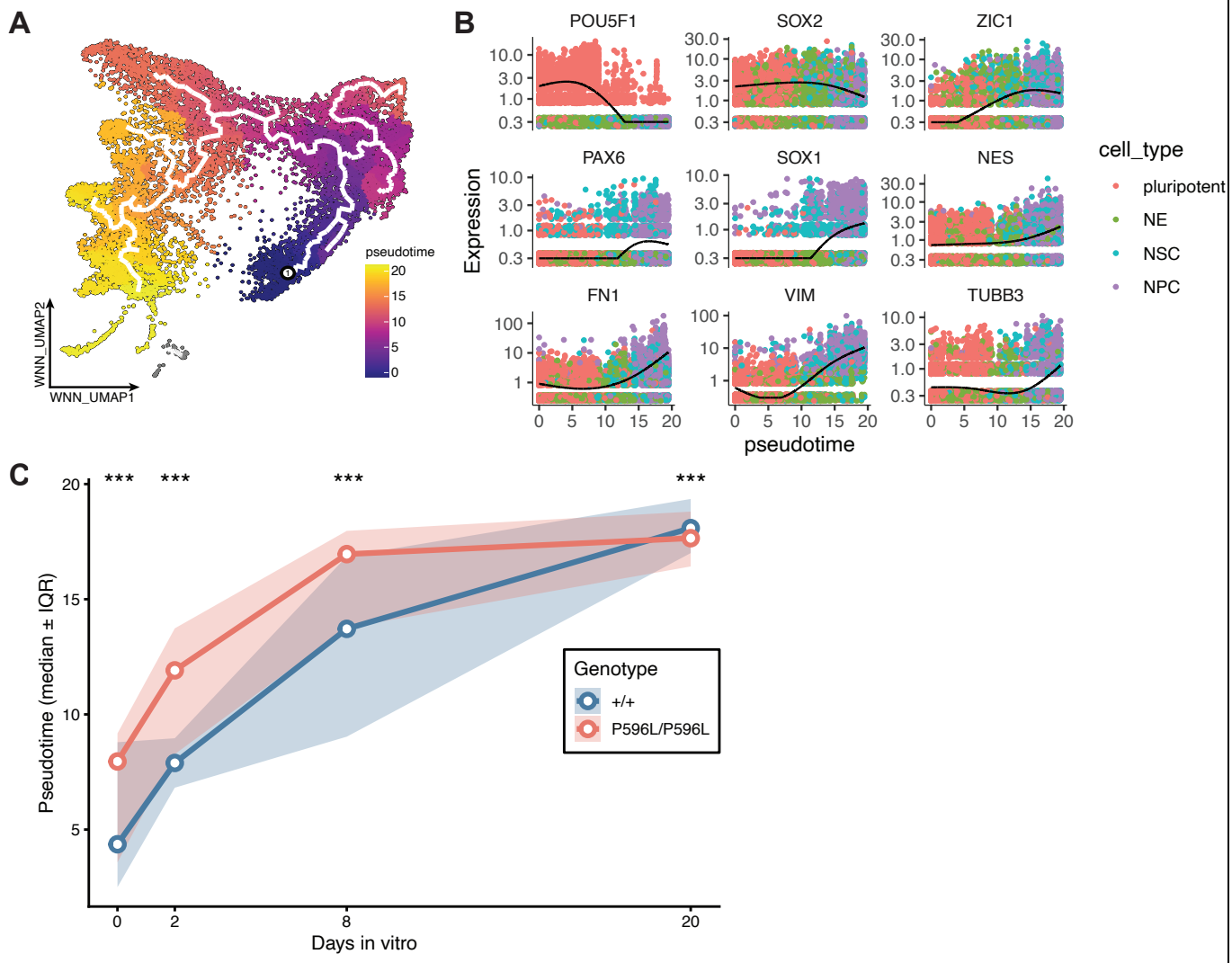

Figure S7. Pseudotime-resolved trajectory and marker dynamics during early neural differentiation reveal a genotype-dependent shift in developmental progression. A. Weighted nearest neighbor (WNN) UMAP of single cells spanning the differentiation series, colored by inferred pseudotime and overlaid with the fitted principal trajectory. **B.** Expression of canonical stage markers plotted as a function of pseudotime for pluripotency (e.g., *POU5F1*, *SOX2*), early neuroectoderm/NSC programs (e.g., *PAX6*, *SOX1*, *NES*, *ZIC1*), and later neural/NPC-associated genes (e.g., *VIM*, *FN1*, *TUBB3*). **C.** Distribution of pseudotime across profiled DIV show an early shift toward later pseudotime in P596L/P596L that diminishes by later timepoints ($p < 2.2e\text{-}16$).

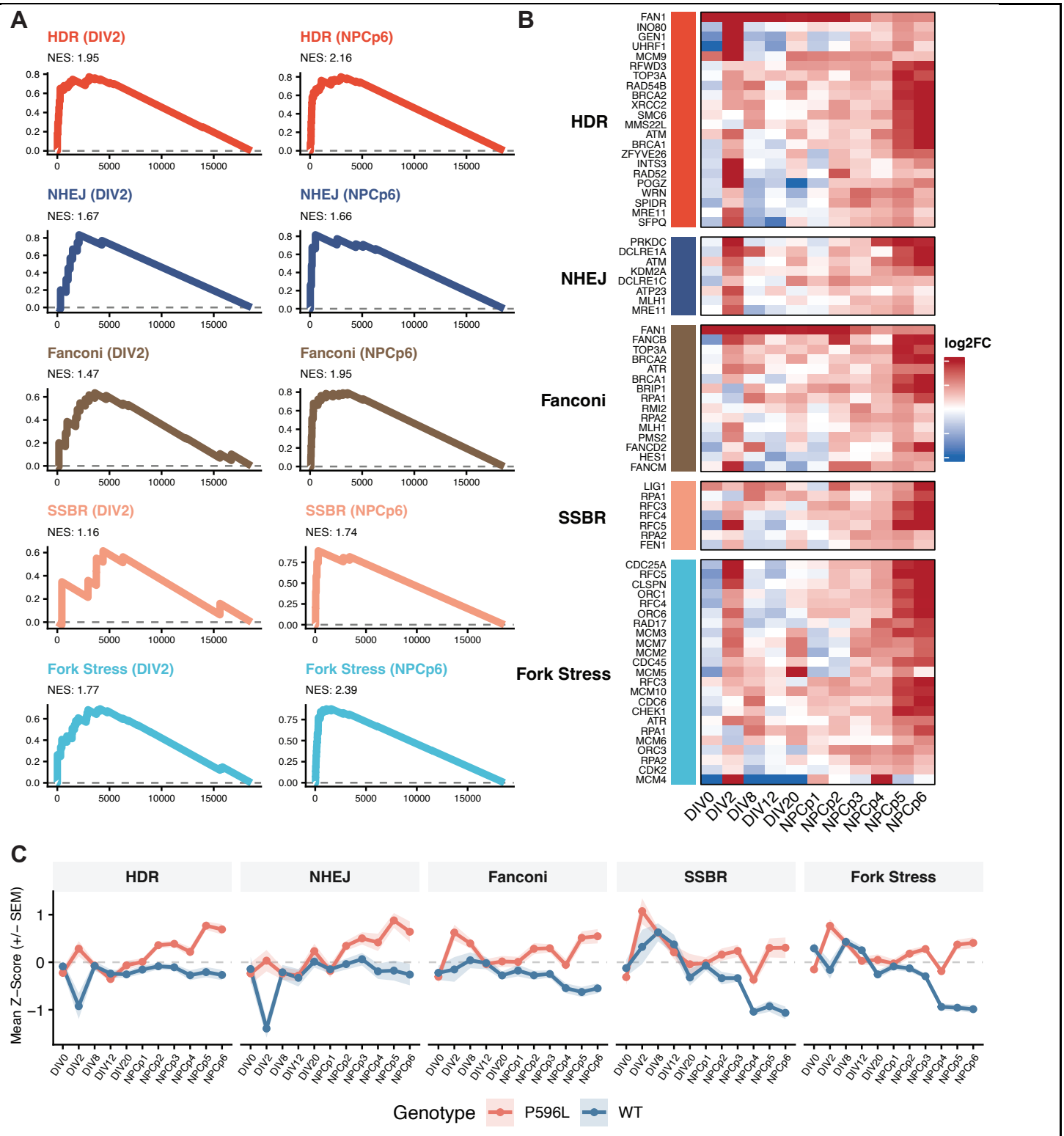

Figure S8. Coordinated upregulation of DNA damage response and replication stress pathways in SETD1A P596L during neural differentiation. A. Gene set enrichment analysis style enrichment plots for each pathway at pluripotency exit (DIV2) and late NPC passage (NPCp6), showing running enrichment score across the ranked gene list and reporting normalized enrichment score (NES) for each comparison. **B.** Differential expression for member genes within each pathway module, plotted as log2 fold-change (P596L/P596L vs +/+) across DIV and NPC passages (red, higher in P596L; blue, lower in P596L). **C.** Mean pathway activity across neural induction and serial passaging for five DNA repair/replication stress gene modules: homology-directed repair (HDR), non-homologous end joining (NHEJ), Fanconi/ICL repair, single-strand break repair (SSBR), and replication fork stress.

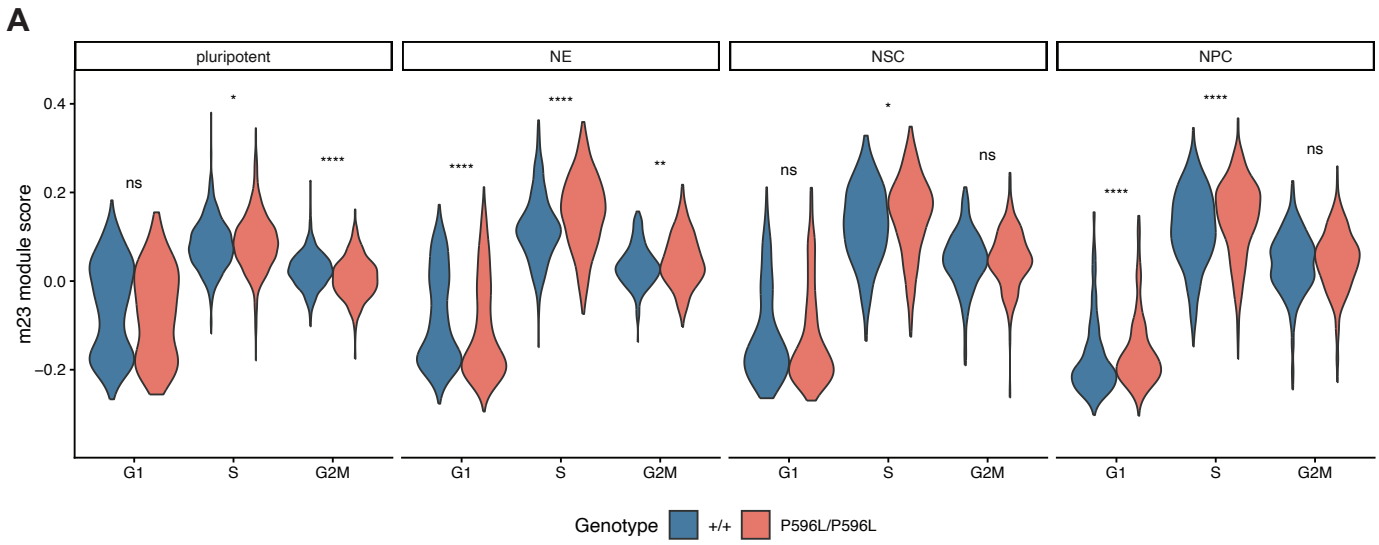

Figure S9. Cell-cycle dependence of the m23 transcriptional program across early neural lineages. A. m23 module score stratified by cell-cycle phase within annotated cell populations. Statistical comparisons of m23 scores across cell-cycle phases within each cell population are annotated above the corresponding groups (ns, not significant; *P<0.05; ****P<0.0001).

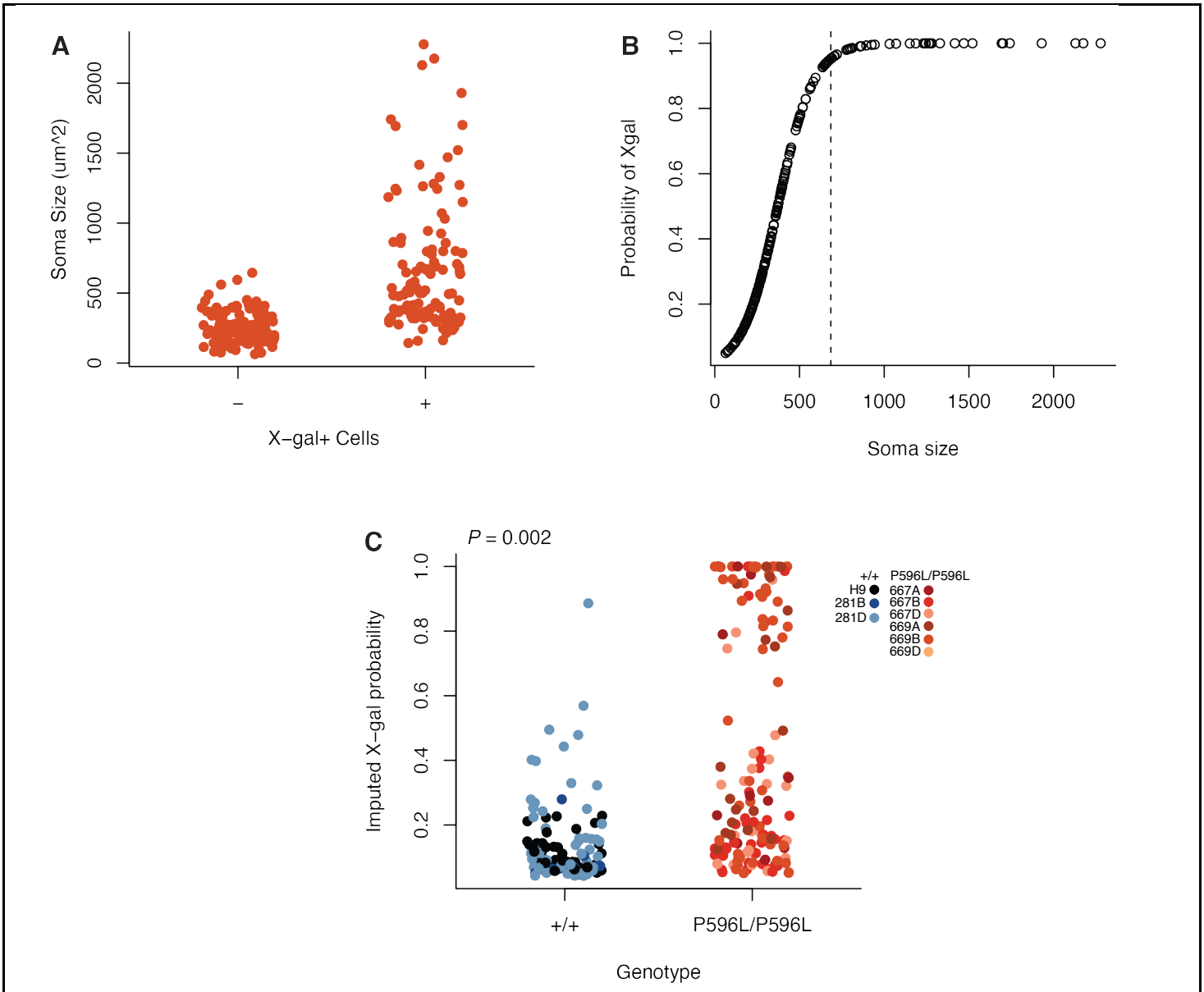

Figure S10. Soma size predicts X-gal staining in senescent cells. **A.** X-gal+ SETD1A P596L NPCs displayed larger soma sizes compared to X-gal- cells. **B.** Soma size >685 μM^2 strongly predicts X-gal+ stain in NPCs. **C.** An increased proportion of serially passaged SETD1A P596L NPCs display senescent morphology based on enlarged soma >685 μM^2.