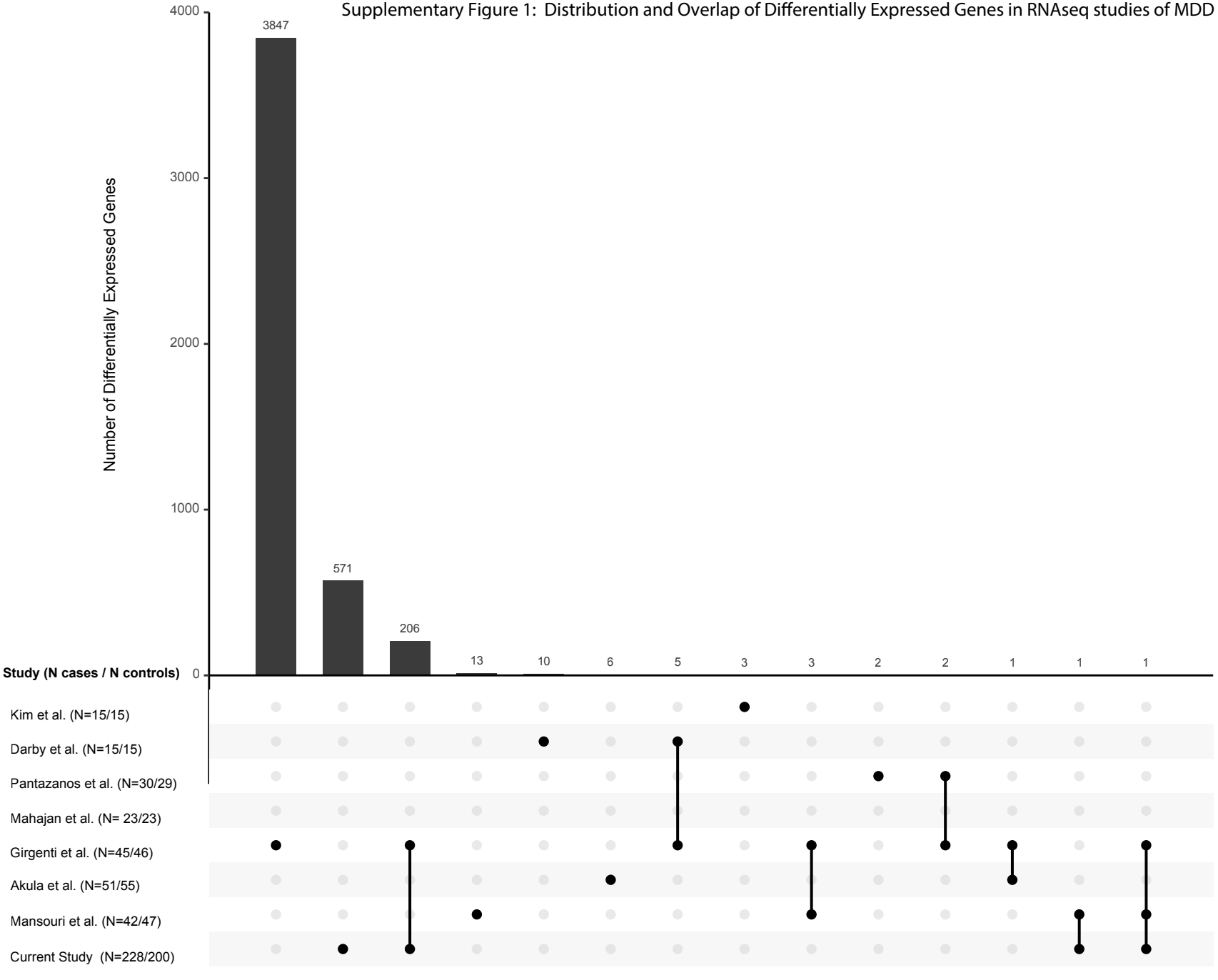
Supplementary Table 1: Summary of RNA sequencing Studies in Major Depressive Disorder

| *Study* | *Pubmed ID* | *Year* | *Tissue* | *Sample* | *Assay/ Analysis* | *N per Group (MDD / Controls)* | |
|---|---|---|---|---|---|---|---|
| *Kohen et al.* | 24594777 | 2014 | Dentate Gyrus | Stanley Brain Collection / UW Neuropathology Brain bank | RNAseq /(ABI SOLiD 4) Multiple DGE analyses | 17 / 29 | |
| *Kim et al.* | 26077692 | 2016 | Hippocampus | Stanley Brain Collection | RNAseq | 15 / 15 | MDD vs Control 3 genes FDR < 5% |
| *Darby et al.* | 27622934 | 2016 | OFC | Stanley Brain Collection | RNAseq | 15 / 15 | MDD vs Control 16 genes FDR < 5% |
| *Labonte et al.* | 28825715 | 2017 | DLPFC, NAc, OFC, anterior insula, ACC, ventral subiculum | Douglas Mental Health Institute / UT Southwestern brain | RNAseq (sex-stratified) DGE/limma | 26 / 22 | Sex-stratified DGE (nominal P > 0.05) |
| *Pantazatos et al.* | 27528462 | 2017 | DLPFC | New York State Psychiatric Institute | RNAseq DGE/DESeq2 | 30 / 29 | MDD vs Control 4 genes FDR < 5% |
| *Ramaker et al.* | 28754123 | 2017 | DLPFC, ACC, NAc | University of California Irvine / Pritzker | RNAseq | 24 / 24 | MDD vs Control No gene FDR < 5% |
| *Mahajan et al.* | 29175309 | 2018 | Dentate Gyrus | Cuyahoga County Medical Examiner's Office | RNAseq DESeq2 | 23 / 23 | MDD vs Control 30 genes FDR < 5% |
| *Girgenti et al.* | 33349712 | 2021 | DLPFC, OFC, dACC, sACC | National Center for PTSD Brain Bank / University Pittsburg | RNAseq DGE/DESeq2 | 45 / 46 | sACC MDD vs Con (4065 genes FDR < 5%) |
| *Akula et al.* | 33349712 | 2021 | sACC | NIMH Human Brain Bank | RNAseq DGE/DESeq2 | 51 / 55 | MDD vs Control (7 genes FDR < 5%) |
| *Shukla et al* | 34686766 | 2022 | PFC | Allegheny County Medical Examiner's Office | RNAseq DGE/DESeq2 | 70 /20 | MDD(all) vs Control No FDR < 5% |
| *Mansouri et al* | 37884562 | 2023 | DLPFC, NAc, OFC, anterior insula, ACC, ventral subiculum | Douglas Mental Health Institute / UT Southwestern brain | RNAseq (sex-stratified) DGE (limma) (inclusive of Labonte et al.) | 42/47 | Sex-stratified DGE (nominal P > 0.05) |

Tissue abbreviations:

OFC: Orbitofrontal Cortex
DLPFC: Dorsolateral Prefrontal Cortex
NAc: Nucleus Accumbens
Anterior Insula: Anterior Insular Cortex (dorsal or subgenual)
ACC: Anterior Cingulate Cortex
Ventral Subiculum: Ventral Subicular Complex

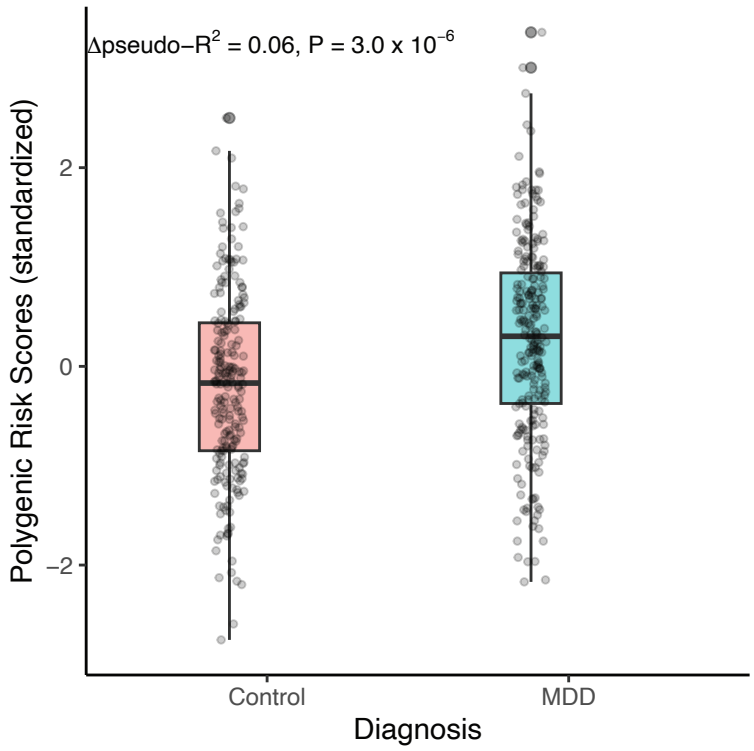
Supplementary Figure 1: Distribution and Overlap of Differentially Expressed Genes in RNAseq studies of MDD



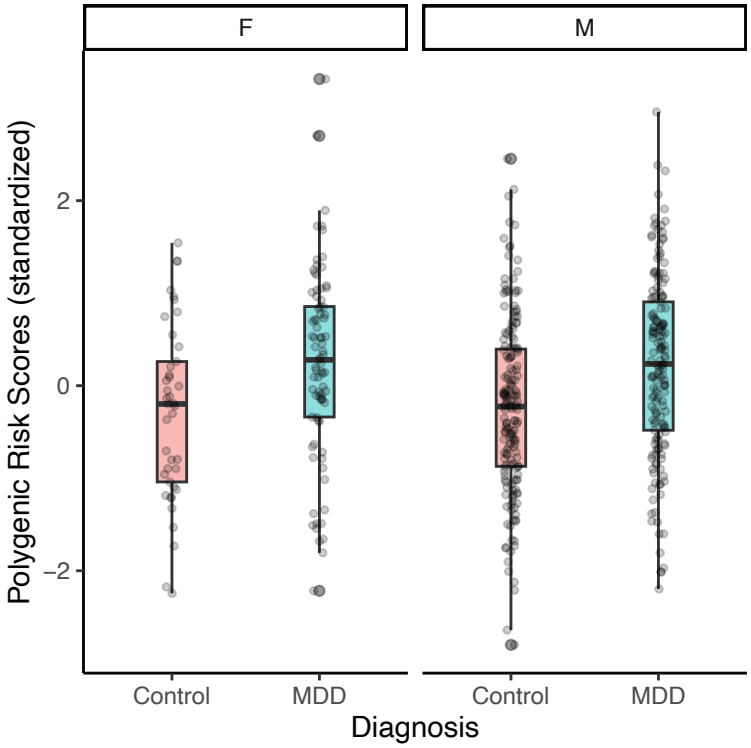

Distribution and Overlap of Differentially Expressed Genes in RNAseq studies of the MDD post-mortem brain

Supplementary Figure 2: Polygenic risk scores by case–control status (A) and stratified by sex (B).

A

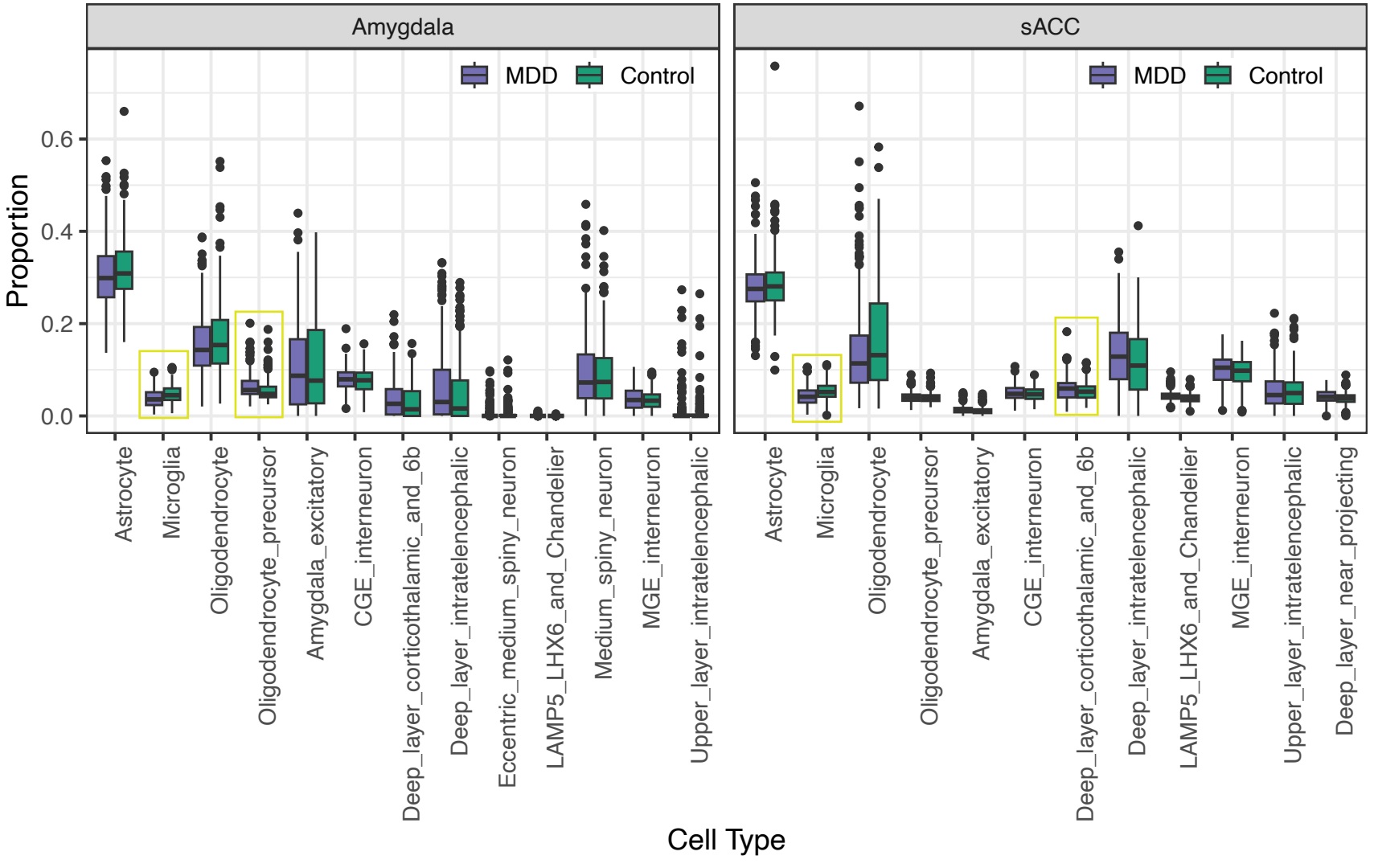



B



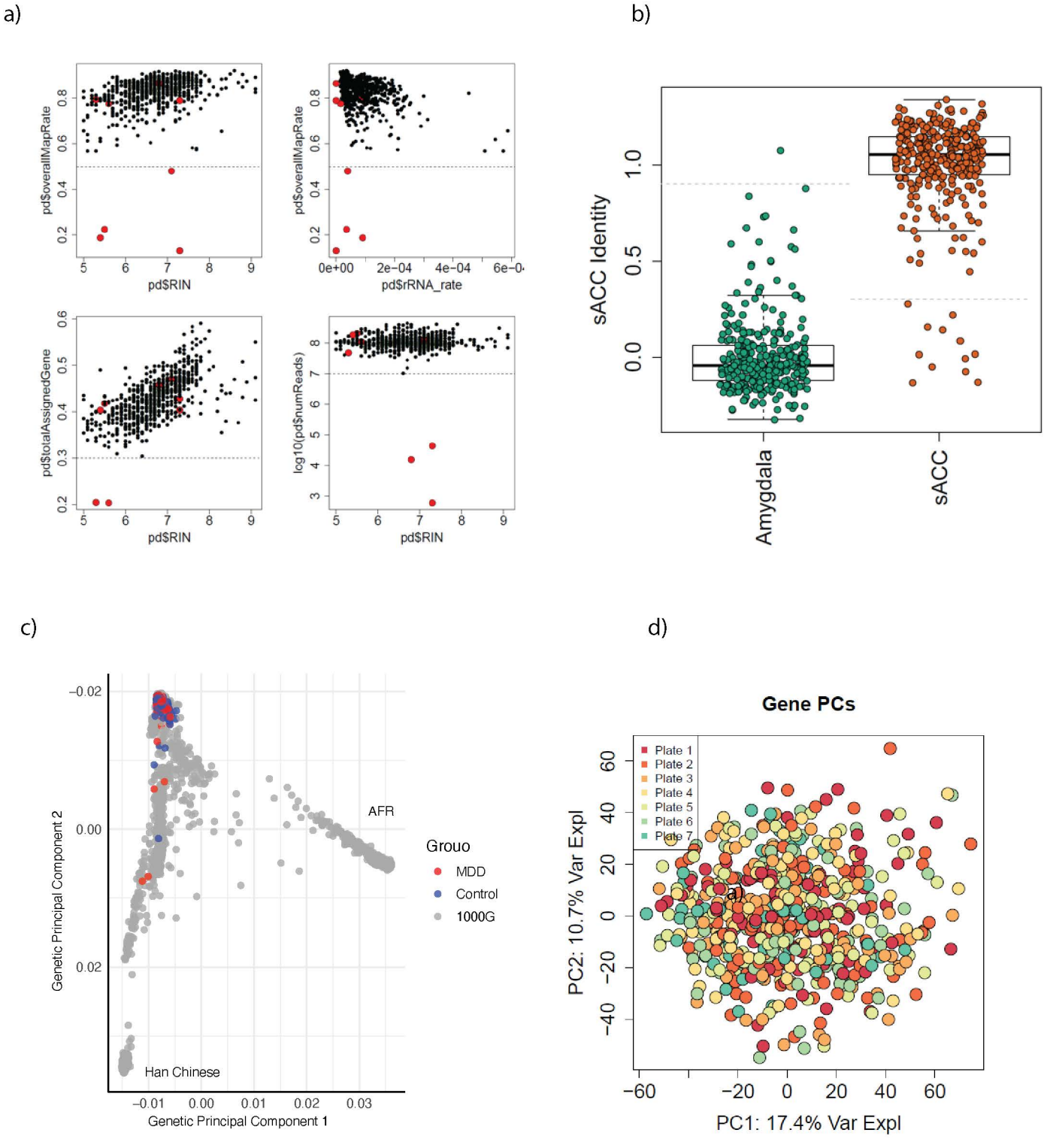

Polygenic risk scores by case–control status (A) and stratified by sex (B).
The top figure additionally shows the proportion of variance explained by case control status (ΔR2) and the P-value of the case-control regression coefficient.

Supplementary Figure 3: Cellular Deconvolution Proportions (significant differences highlighted)



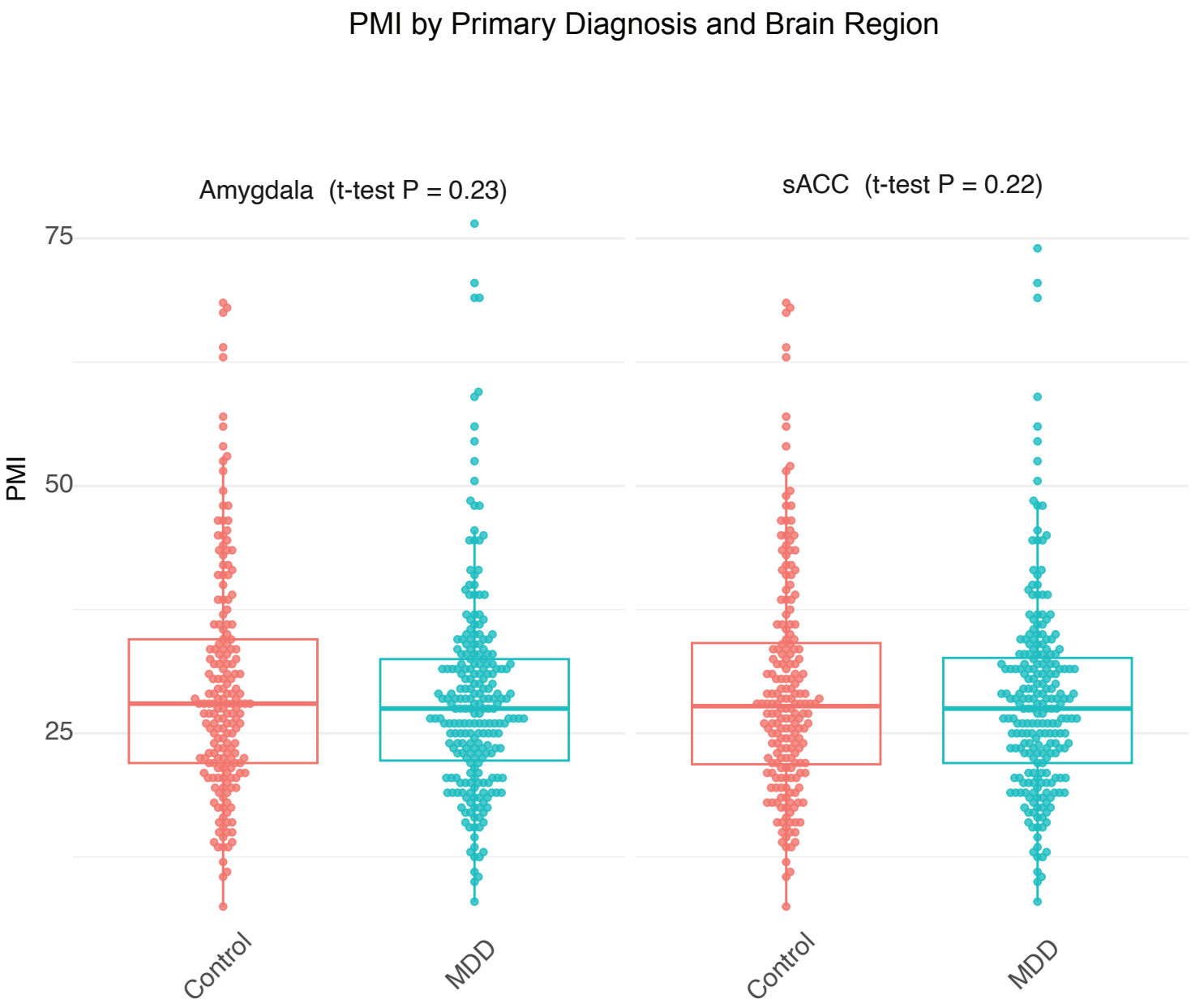

Cellular Deconvolution Proportions on the BRAIN Initiative - Cell Census Network (BICCN) classification using the hspe (hybrid-scale proportions estimation) package. Proportions are plotted by brain region and compared between MDD cases and controls. Proportions with significant case–control differences are highlighted in yellow.

Supplementary Figure 4: Quality Control Metrics



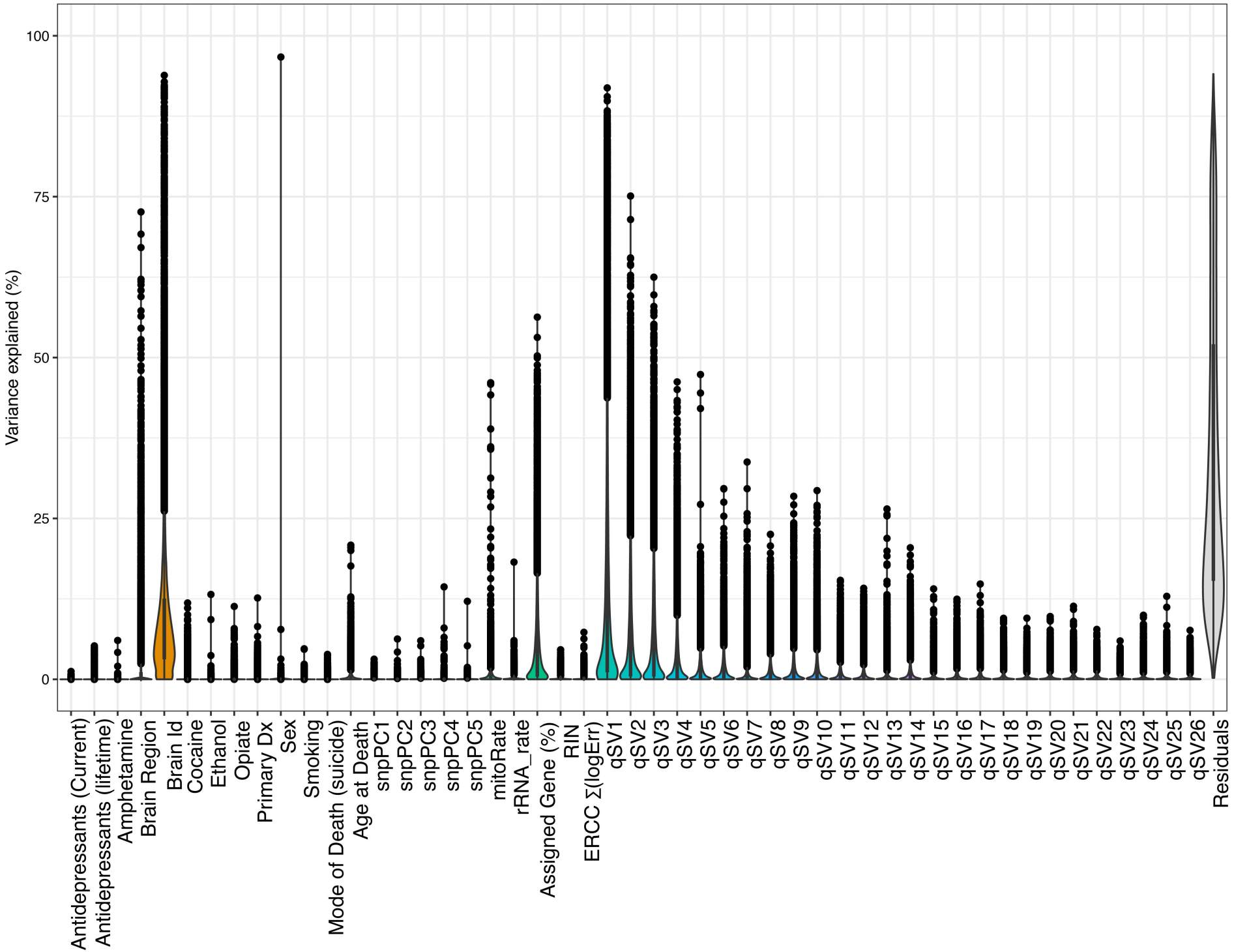

Panel A: Distribution of samples across key QC metrics from Supplementary Dataset 2 (RIN, overall mapping rate, percentage of ribosomal RNA, proportion of reads mapping to genic regions, and total number of reads). Dotted lines indicate boundary thresholds for outlier exclusion.
Panel B: Distribution of samples showing region-specific identity, determined by region-specific genes. Dotted lines indicate samples excluded during quality control.
Panel C: Gene-based principal component analysis, anchored by samples from the 1000 Genomes Project.
Panel D: Distribution of RNA-seq–based expression principal components, showing no evidence of batch effects by sequencing plates.

Supplementary Figure 5: Distribution of Post-Mortem Interval by case-control Status



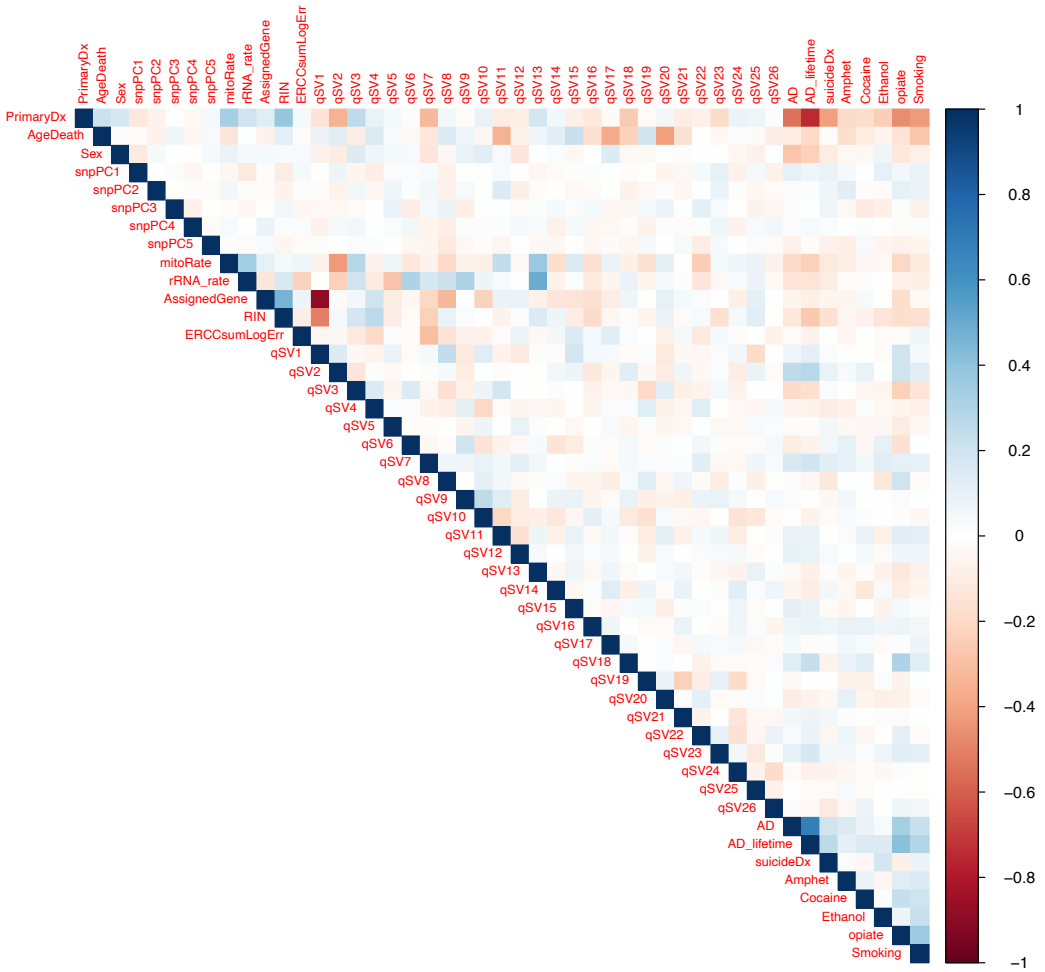

Distribution of post-mortem interval (PMI) by case–control status in the amygdala and sACC. Comparisons with t-test shows no significant difference in PMI between cases and controls.

Supplementary Figure 6: Variance Partitioning Plot of Gene Expression Counts

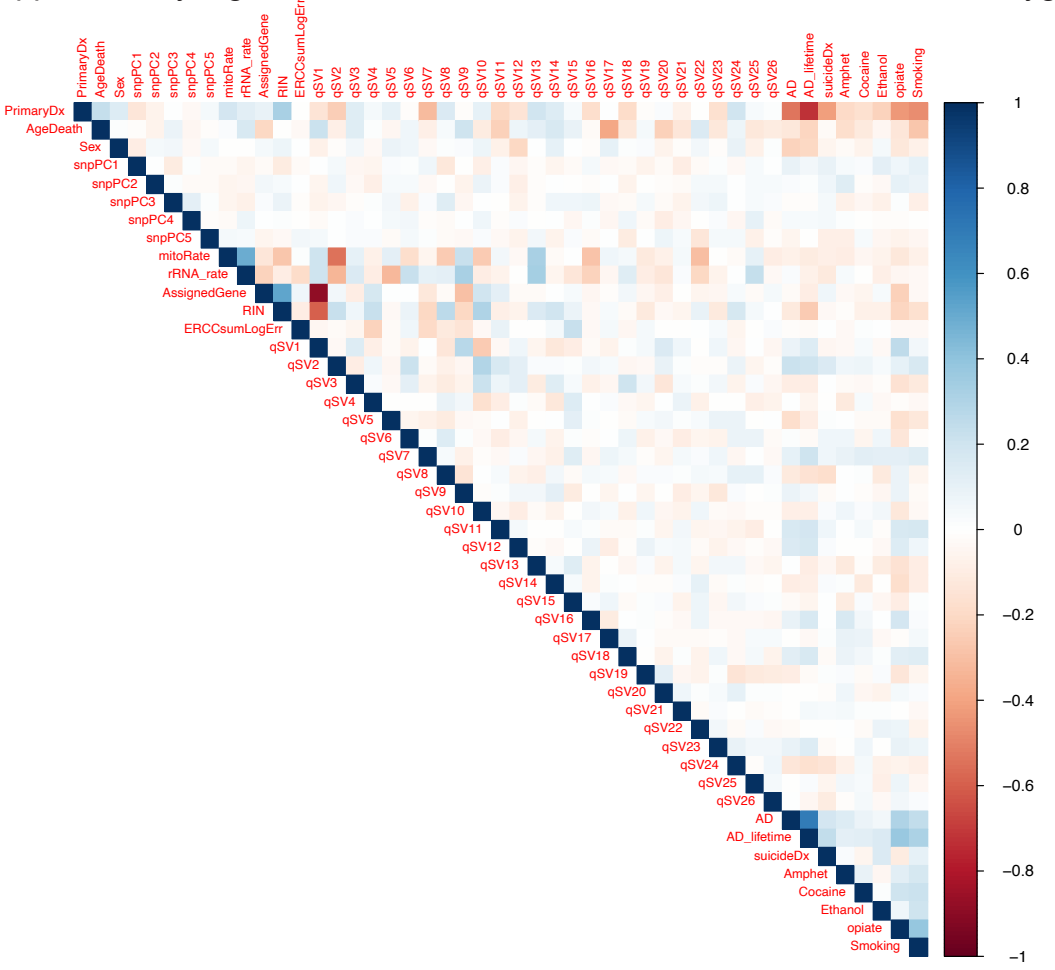



Variance partitioning of gene expression by technical and clinical covariates using the variancePartition R package

Supplementary Figure 7a: Correlation Matrix of Covariates used in the sACC



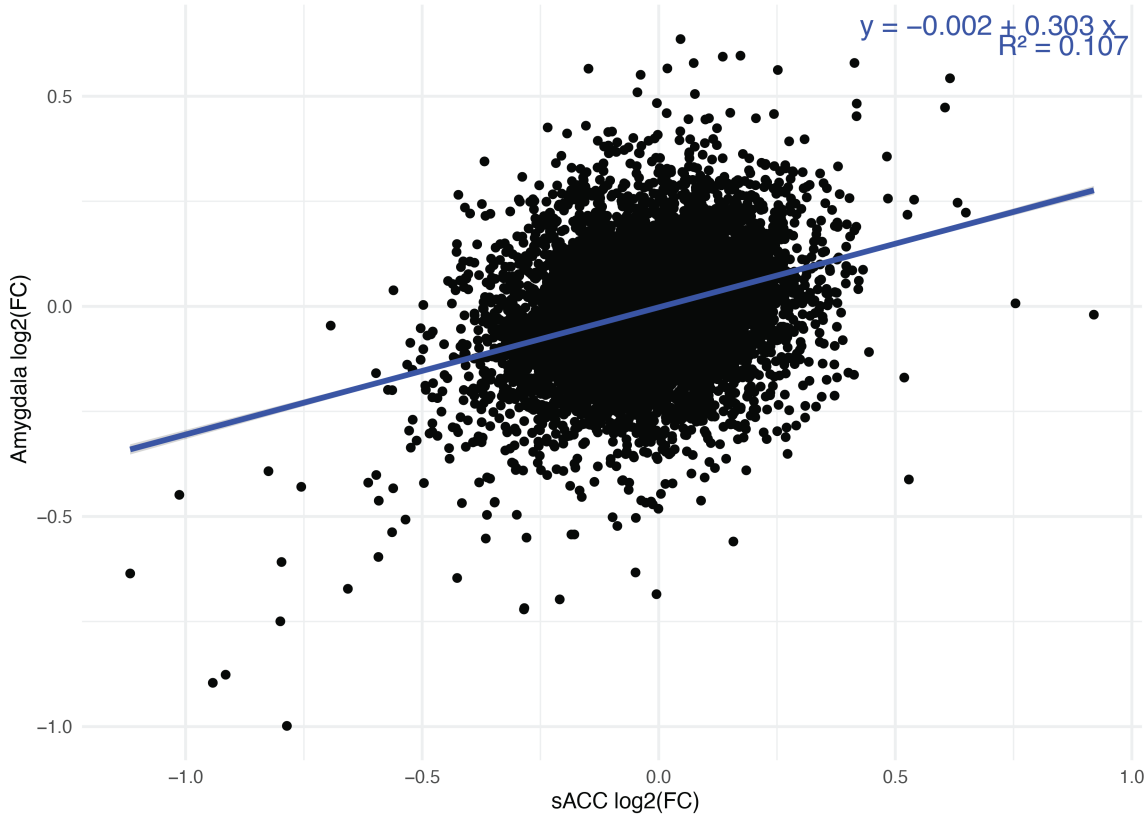

Supplementary Figure 7b: Correlation Matrix of Covariates used in the Amygdala




Correlation matrix of technical, clinical and genetic covariates included in the analyses of the (a) sACC and (b) amygdala

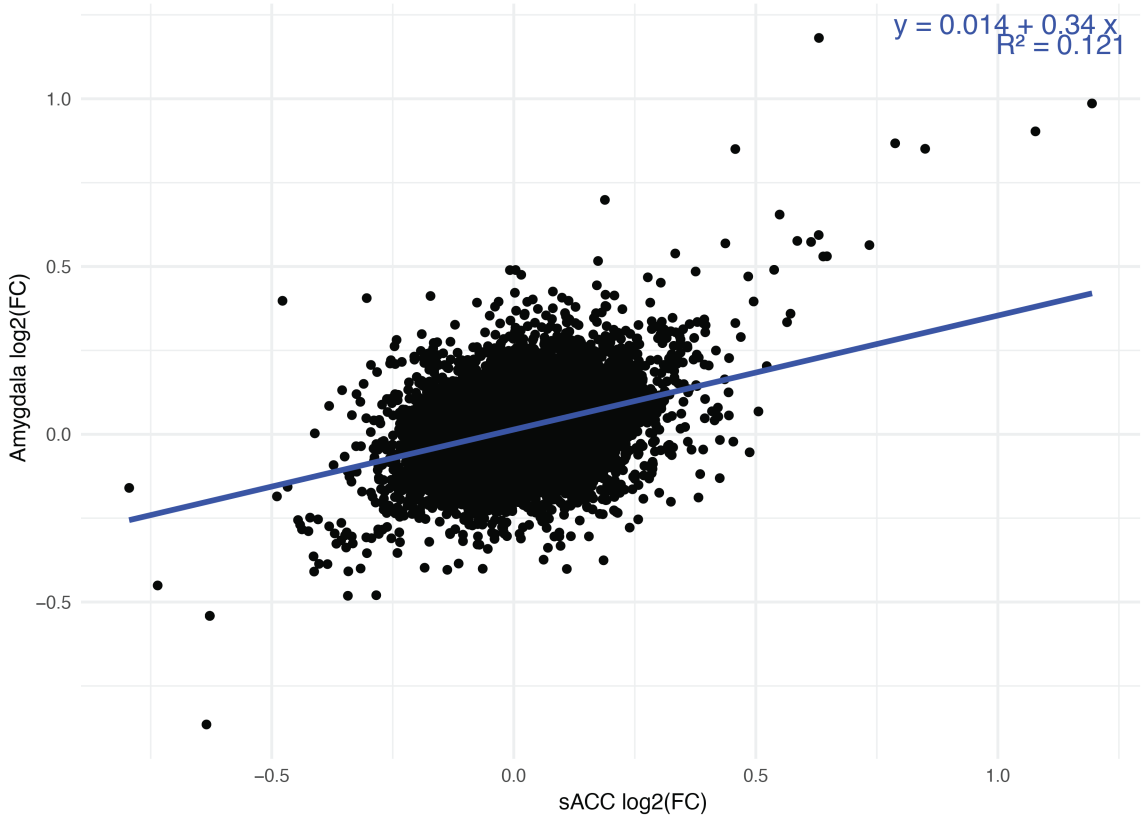
Supplementary Figure 8a:

Comparison of Differential Gene Expression $\log_2$(Fold Change) in the sACC versus the amygdala



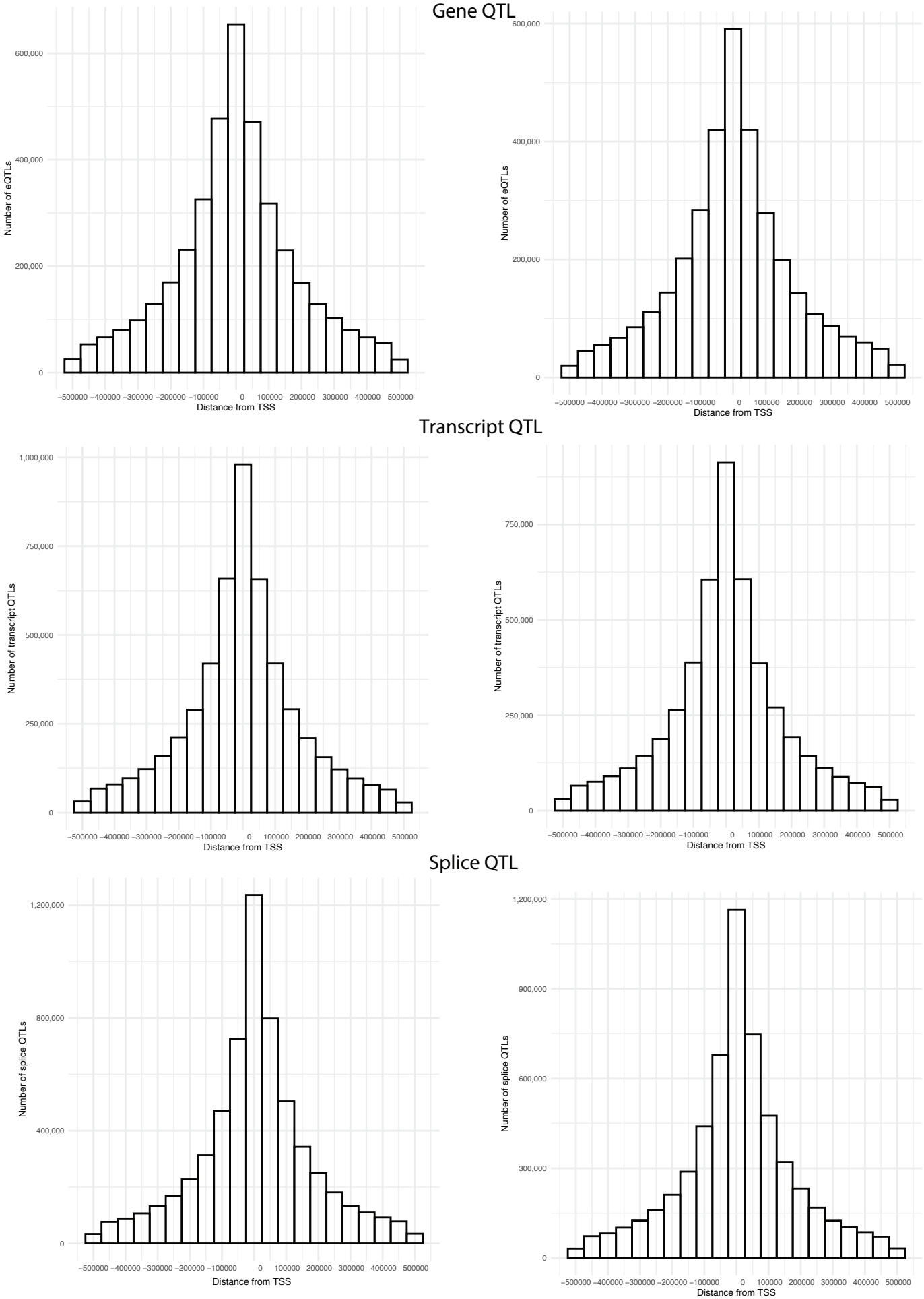

Supplementary Figure 8b:

Comparison of Differential Transcript Expression $\log_2$(Fold Change) in the sACC versus the amygdala



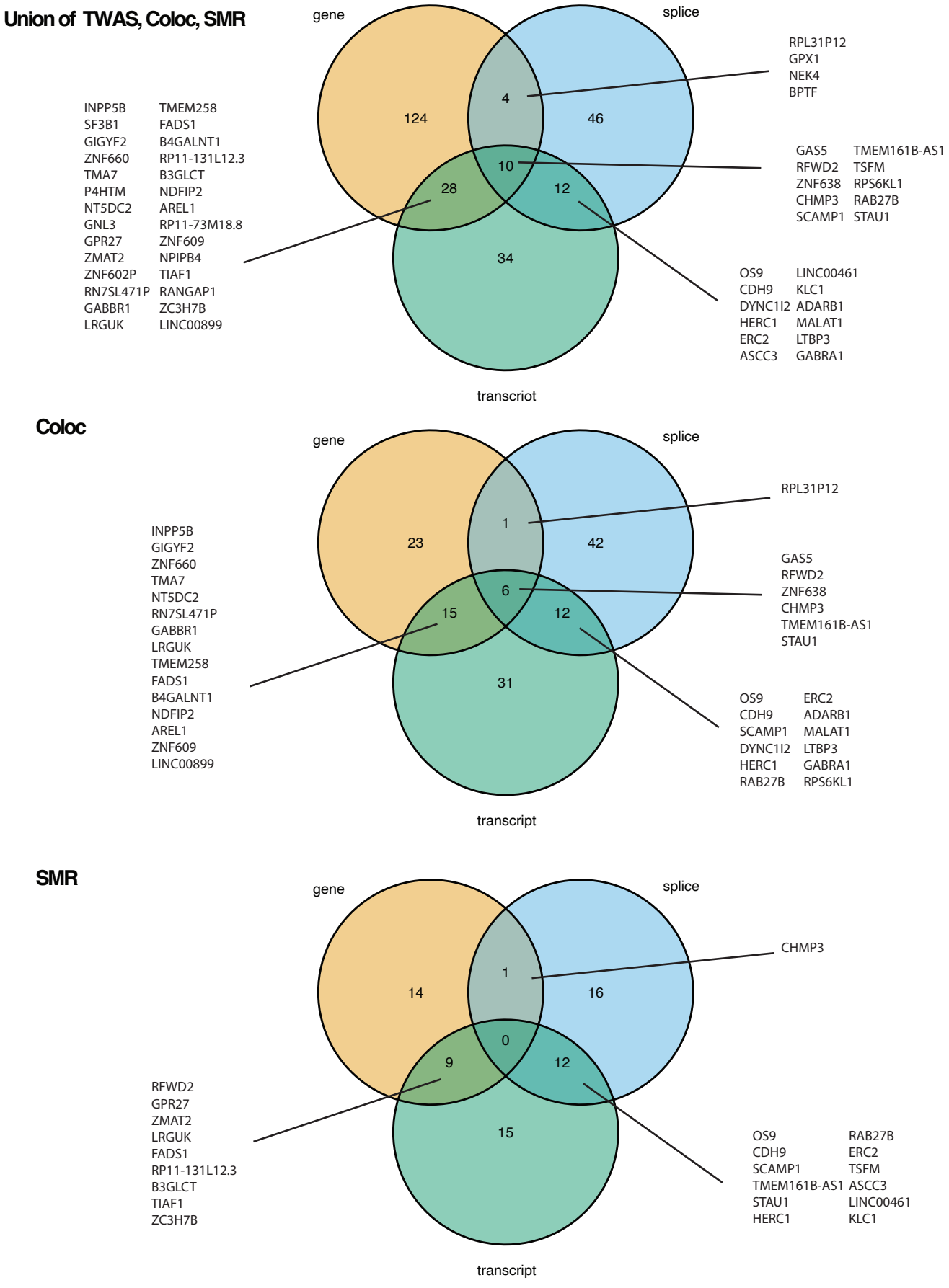

Equations represents parameters estimated by the linear regression model (β coefficients and intercept), along with the coefficient of determination ($R^2$) indicating model fit.

Supplementary Figure 9: Distribution Quantitative Trait Loci relative to the Transcription Start Site



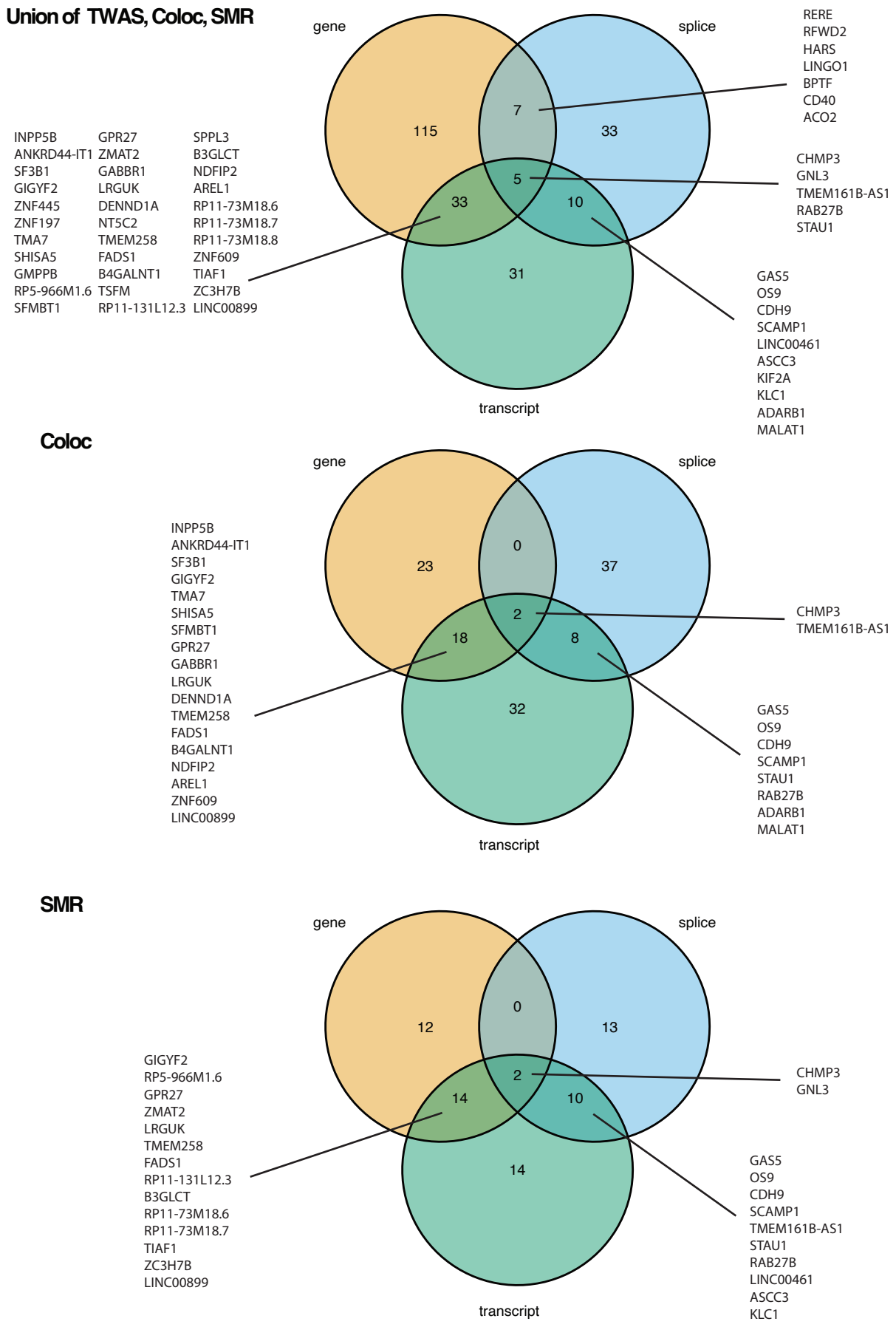

Distribution of quantitative trait loci (QTLs) relative to the transcription start site for gene-, transcript-, and splice-level QTLs in the sACC (left) and amygdala (right)

Supplementary Figure 10a: Overlap of TWAS/QTL associated transcriptional features in the sACC




The top subfigure shows the overlap of genes, splicing clusters, and transcripts identified as significant in TWAS, coloc, or summary-based Mendelian Randomization (SMR) analyses. The middle subfigure highlights significant genes, splicing clusters, and transcripts in coloc analyses (PP.H4 > 0.8), while the bottom subfigure displays the overlap for SMR analyses (marker–feature associations with a Bonferroni-corrected p-value < 0.05).

Supplementary Figure 10b: Overlap of TWAS/QTL associated transcriptional features in the amygdala




The top subfigure shows the overlap of genes, splicing clusters, and transcripts identified as significant in TWAS, coloc, or summary-based Mendelian Randomization (SMR) analyses. The middle subfigure highlights significant genes, splicing clusters, and transcripts in coloc analyses (PP.H4 > 0.8), while the bottom subfigure displays the overlap for SMR analyses (marker–feature associations with a Bonferroni-corrected p-value < 0.05).