APPENDIX

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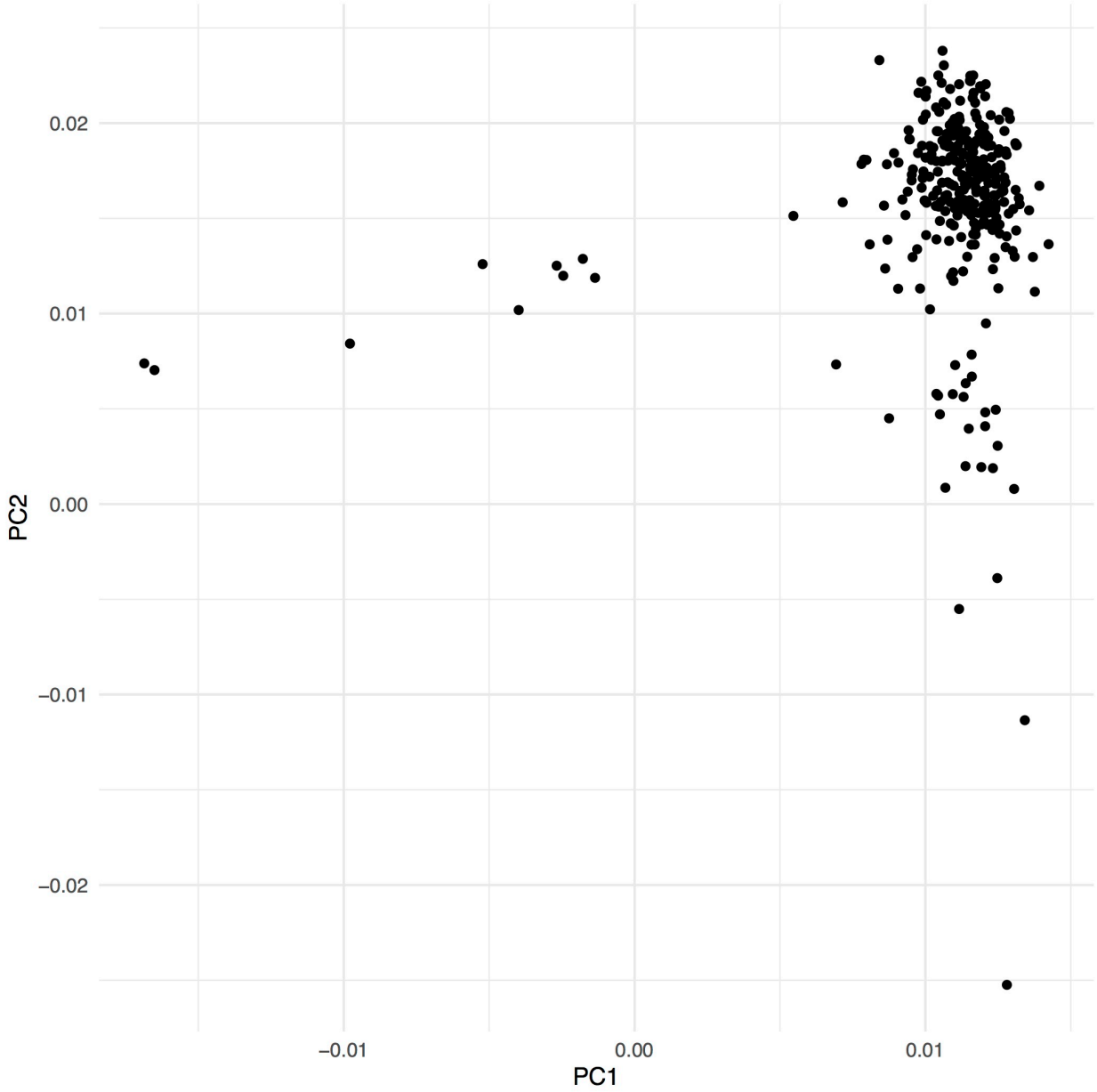
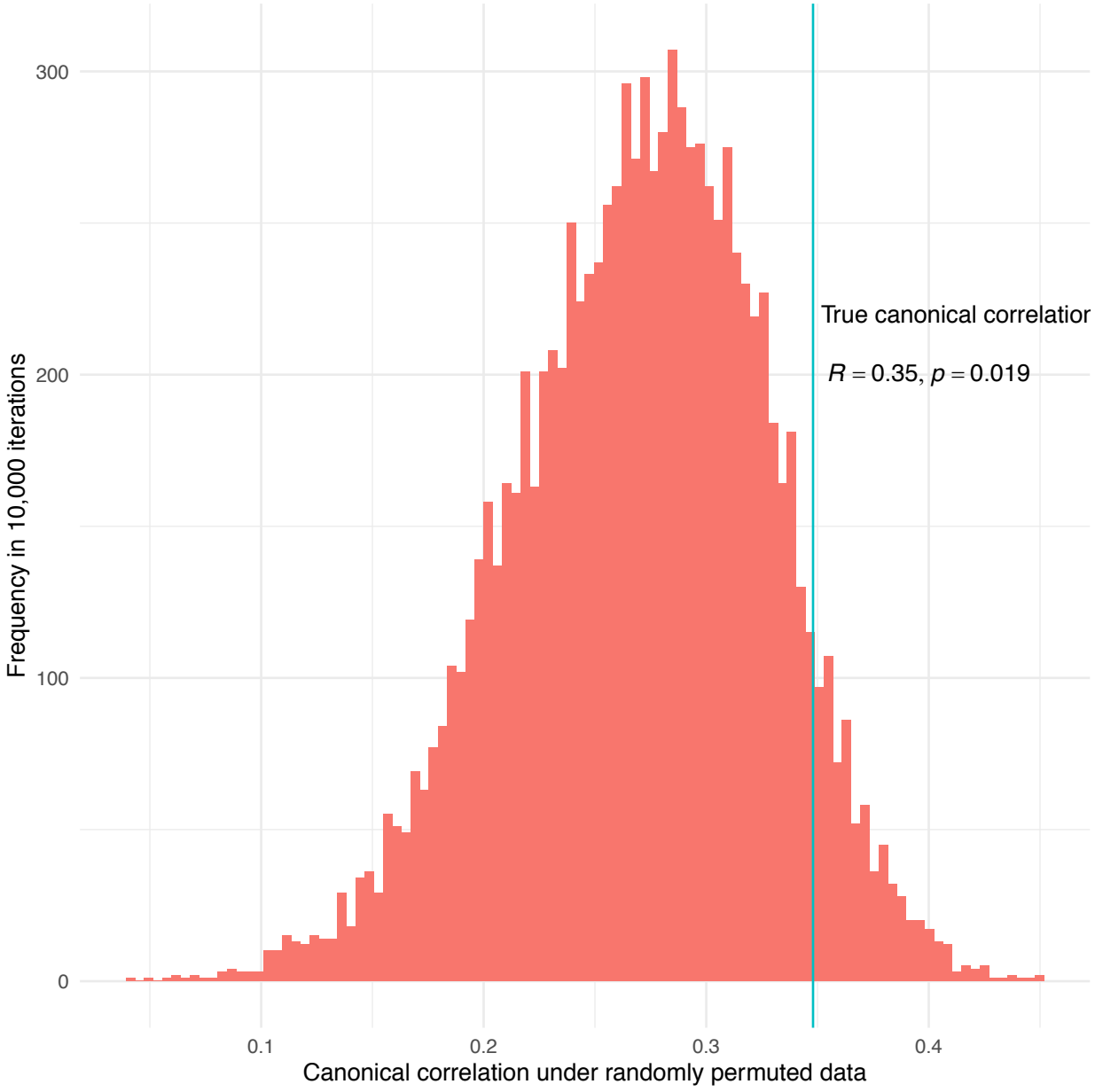
Supplementary Figures:

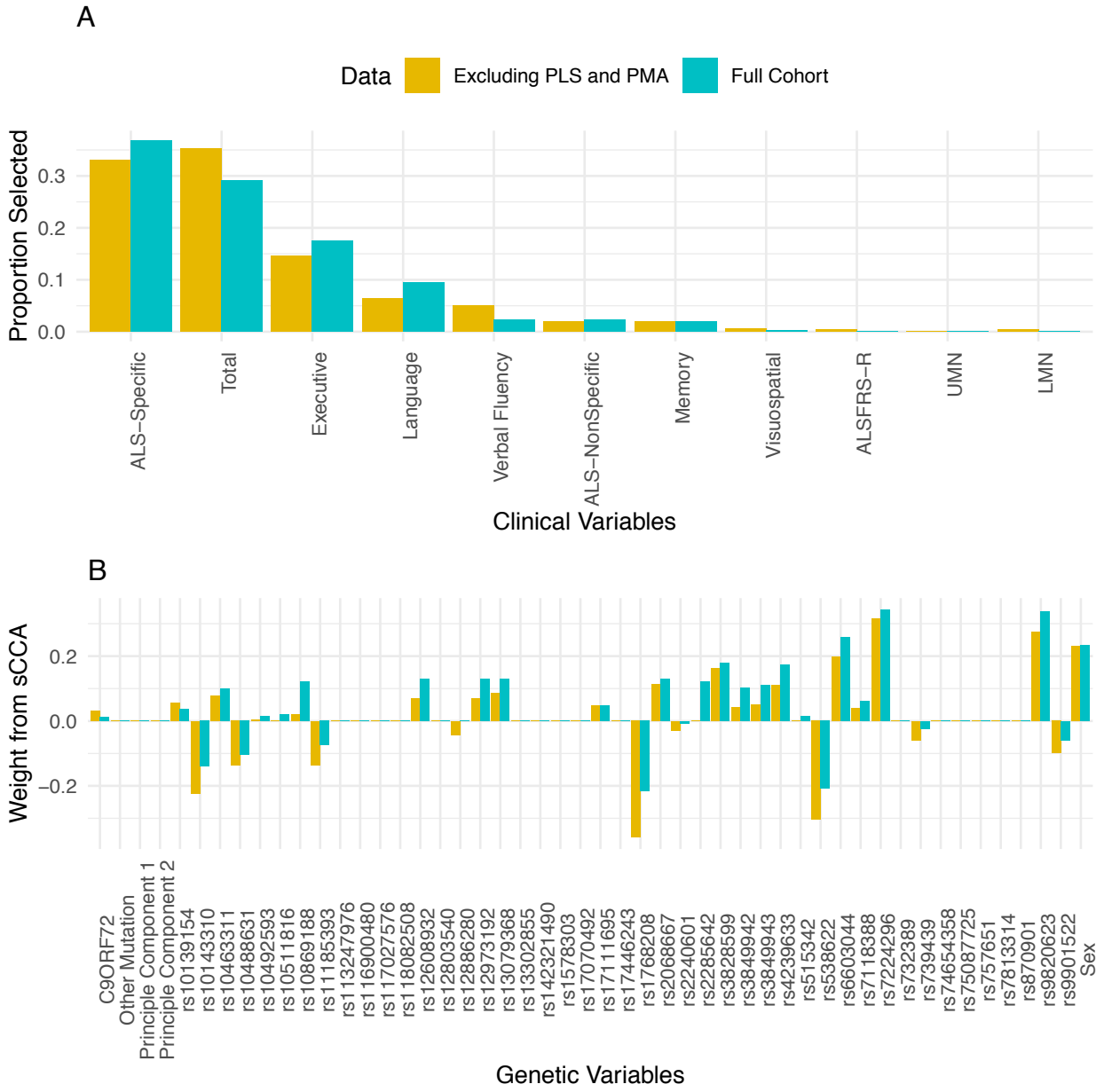
Appendix Figure S1. Principal Components in the CReATe PGB cohort. Scatterplot showing the first principal component plotted against the second principal component from a principal components analysis conducted in the CReATe PGB cohort.



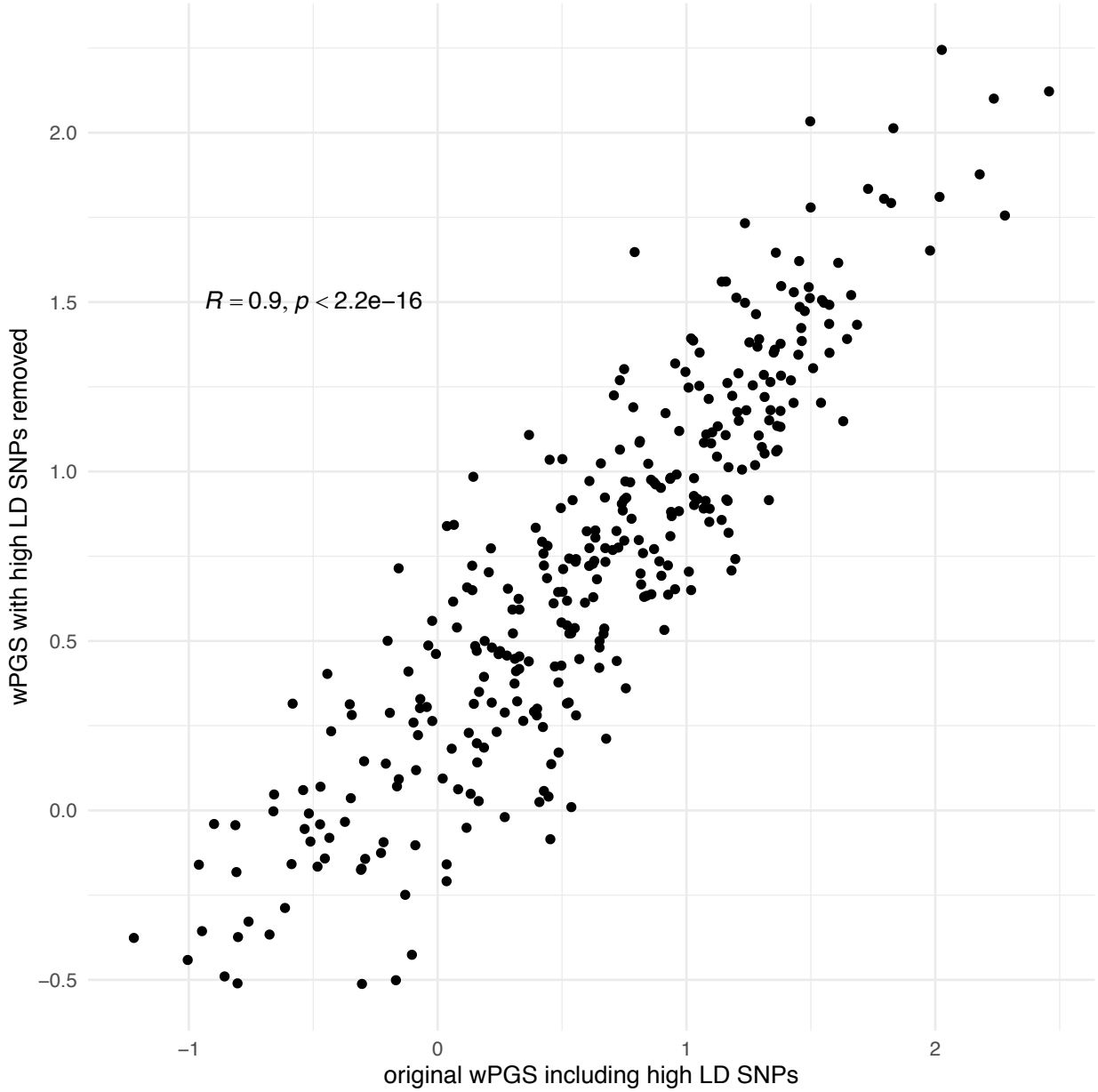
Appendix Figure S2. *p* value calculation for sCCA modeling. Histogram showing the frequency of canonical correlations achieved for sCCA modeling using 10,000 bootstrapped random permutations of the data. The vertical turquoise line denotes the median canonical correlation achieved under sCCA modeling of the true unpermuted data. The *p* value is the proportion of times the median canonical correlation (*R*) for sCCA modeling of the true, unpermuted data was achieved by sCCA modeling of the randomly permuted data.



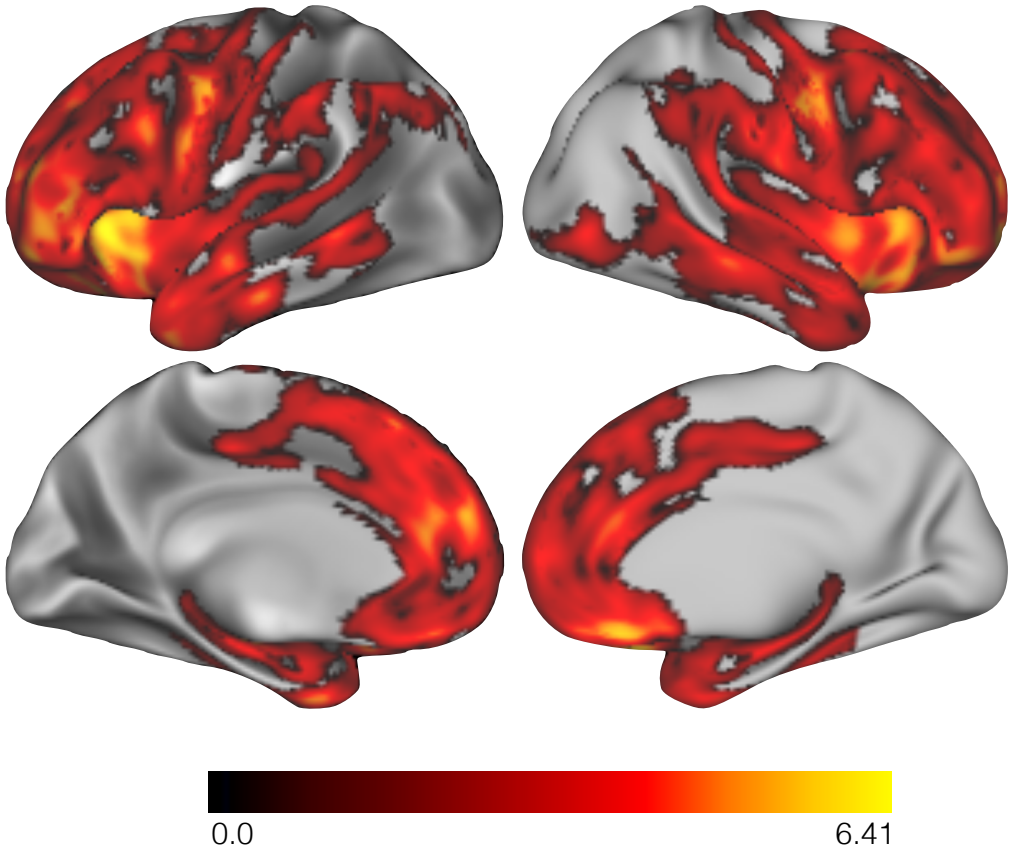
Appendix Figure S3. Variables selected in sCCA modeling excluding patients with primary lateral sclerosis and progressive muscular atrophy.
A) Bar graphs demonstrating the proportion of times out of 10,000 iterations that each of the 11 clinical variables were selected by sCCA under true modeling (turquoise) and modeling under the null hypothesis (coral).
B) Bar graphs demonstrating the number of times out of 10,000 randomly-bootstrapped sCCAs that each of the 45 SNPs were selected by sCCA under true modeling (turquoise) and modeling under the null hypothesis (coral). SNPs are organized according to prior genome-wide association with ALS or joint association with ALS and FTD.



Appendix Figure S4. wPRS calculated with and without variants in high LD. Scatterplot depicting Pearson's correlation between the wPRS calculated using all genetic variables and the wPRS calculated excluding SNPs in high linkage disequilibrium.



Appendix Figure S5. Reduced cortical thickness in ALS patients relative to healthy controls. ALS patients from the UPenn Biobank neuroimaging cohort displayed widespread cortical thinning relative to age, sex, and education-matched healthy controls in the frontal and temporal lobes. The heatmap indicates the associated T-statistic for each voxel, with light yellow representing the highest value.



Appendix Figure S6. Magnitude of TDP-43 pathology in ALS cases at autopsy relative to wPRS. Beeswarm boxplots of ordinal measures of TDP-43 pathology in ALS cases the UPenn Biobank autopsy cohort relative to wPRS in the cingulate cortex, motor cortex, middle frontal cortex, superior / middle temporal cortex, and hippocampus. The central bands indicate the median, the box indicates the interquartile range (IQR) between the first and third quartiles, and the upper and lower whiskers indicate the largest or smallest value no further than the IQR multiplied by 1.5. For each brain region each data point represents a unique case.