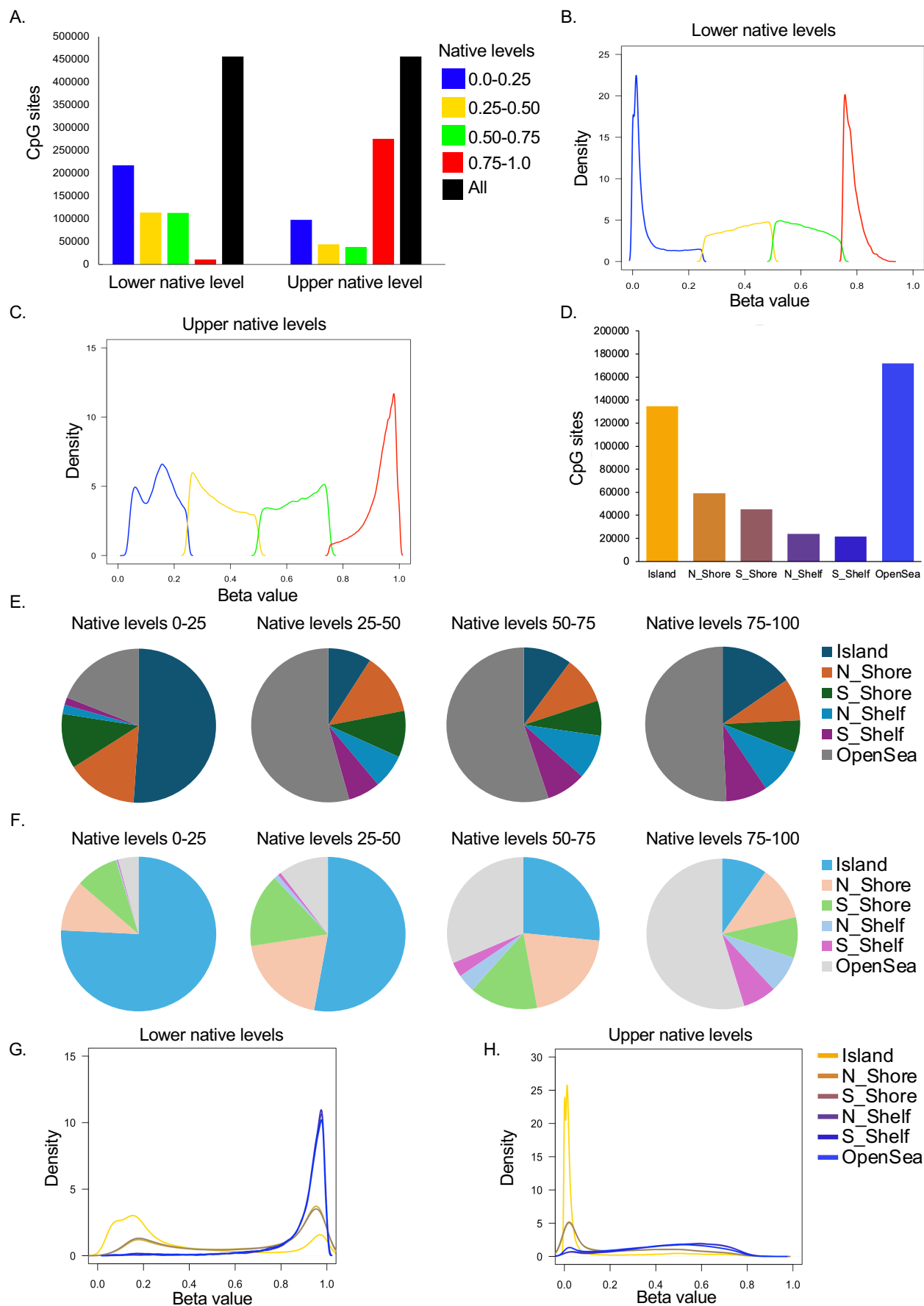
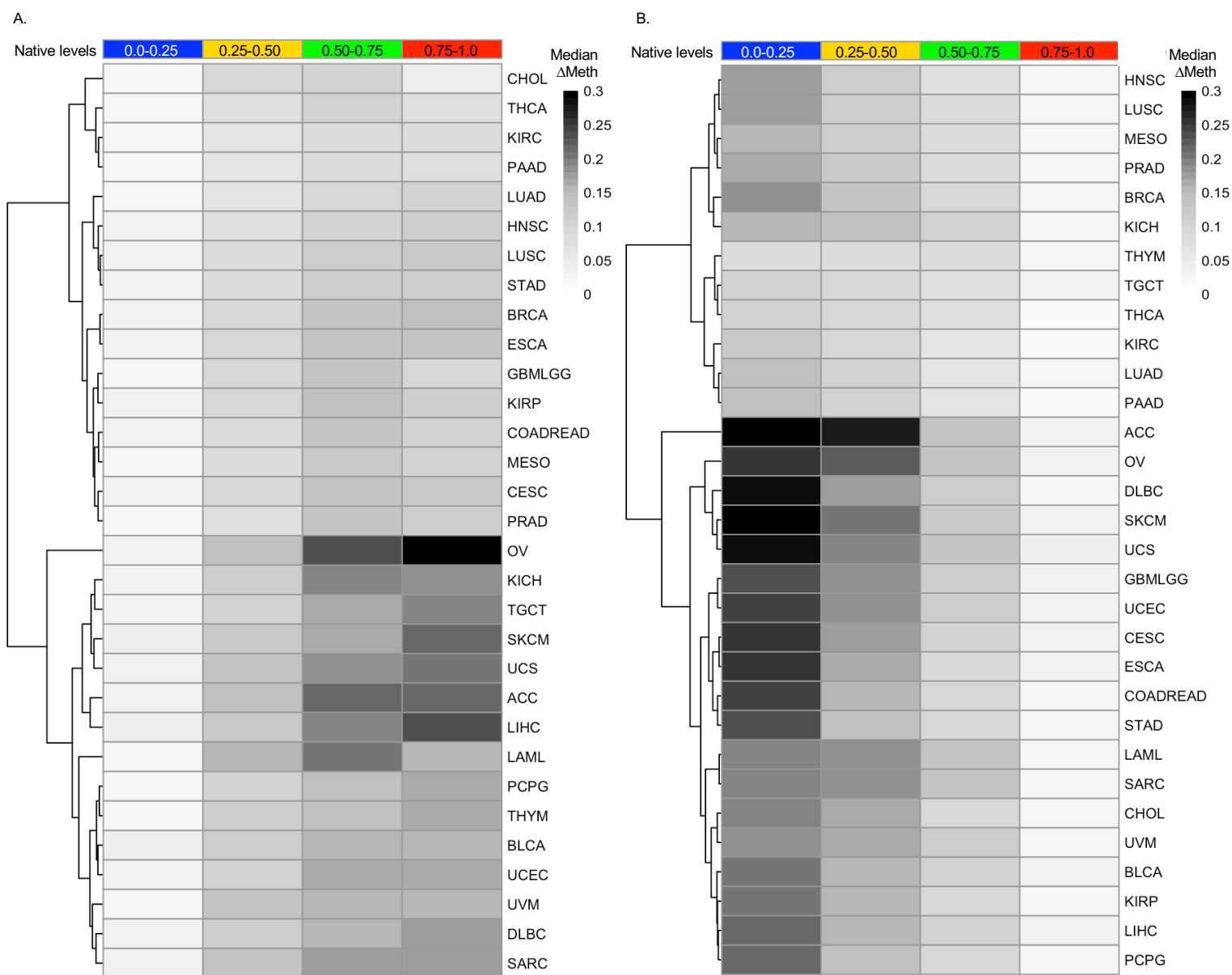
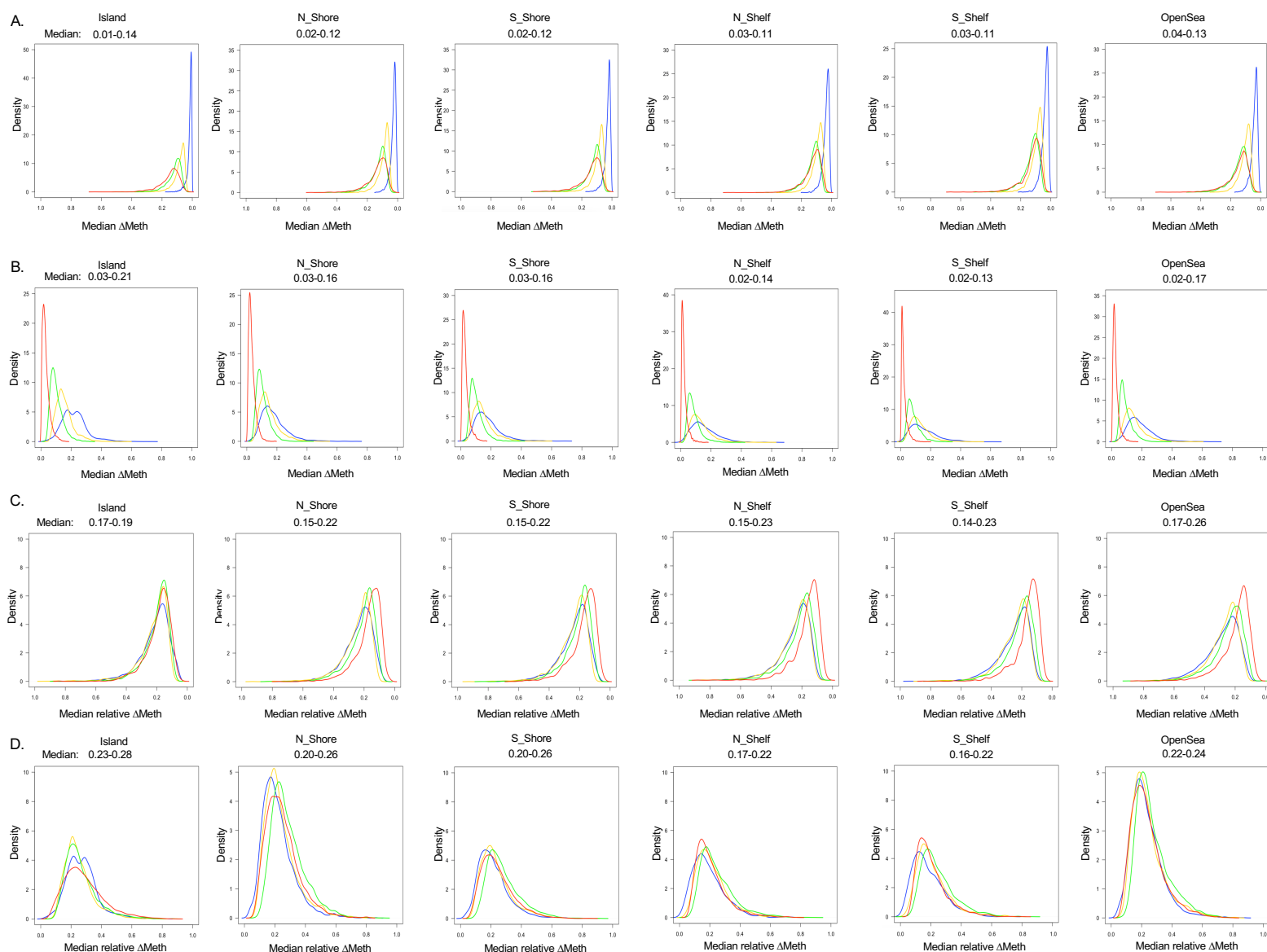




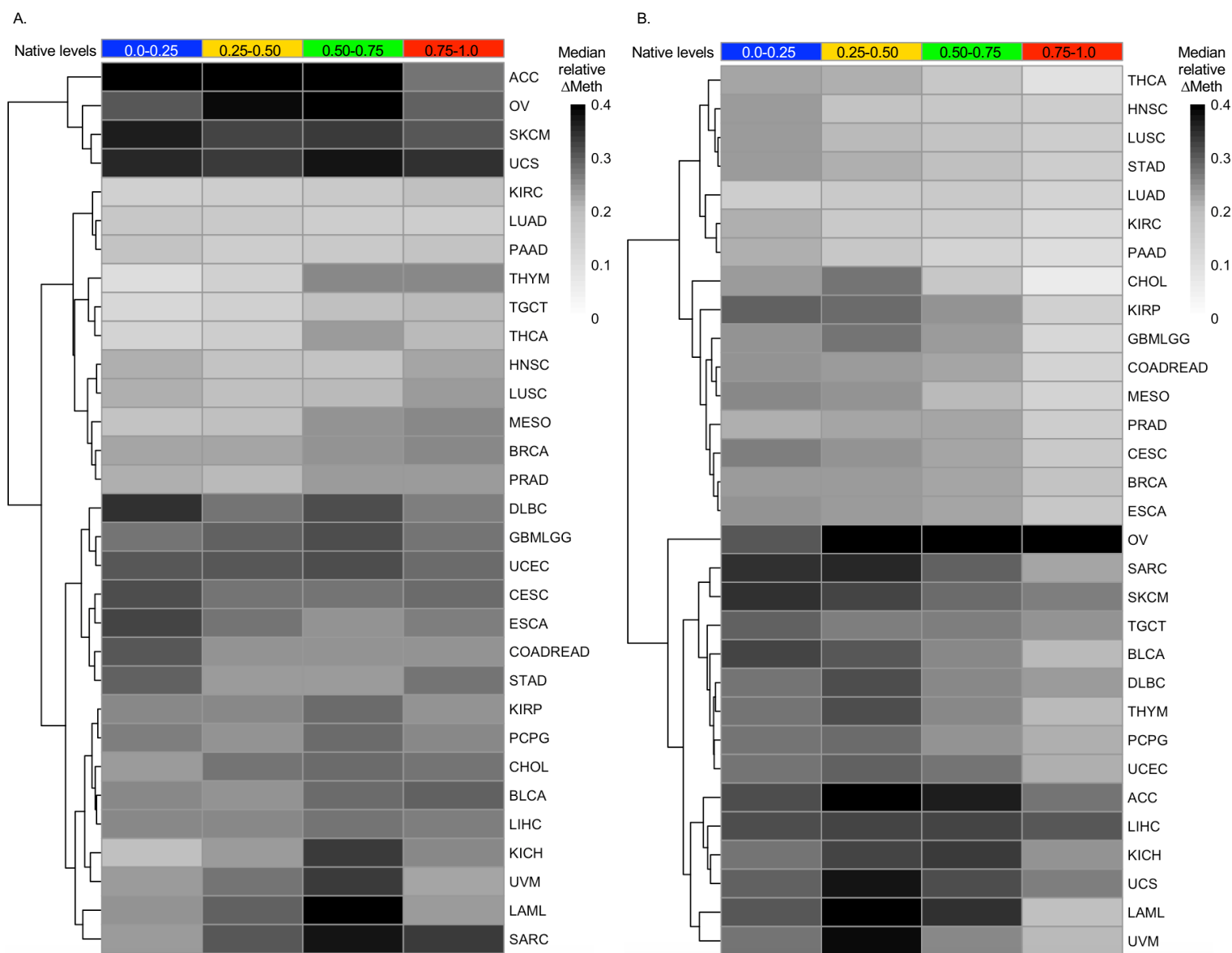
Supplemental Figure S1. A. Bar plot showing the number of CpG sites with lower and upper native DNA methylation levels separated into four quantiles. Density plots showing the distribution of the native DNA methylation levels in the **B.** lower and **C.** upper direction. **D.** Bar plot showing the number of CpG sites for the different genomic regions. Pie charts showing the proportion of different genomic regions in the **E.** lower and **F.** upper direction of the CpG sites with varying quantiles of native DNA methylation. Density plots showing the native DNA methylation levels within the different genomic regions in the **G.** lower and **H.** upper direction.



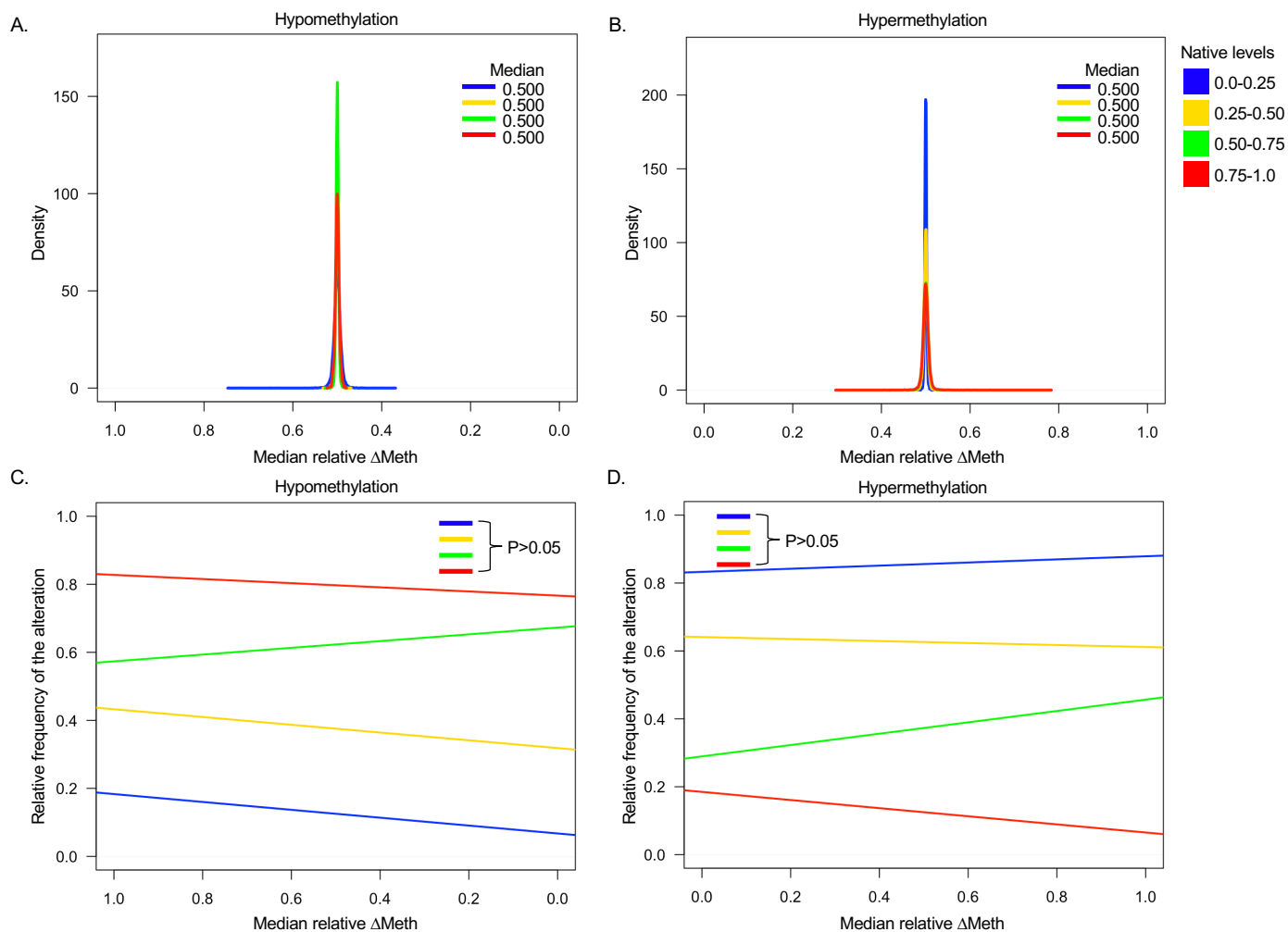
Supplemental Figure S2. Heatmap of the median ΔMeth of the CpG sites with varying levels of native DNA methylation in the **A.** hypomethylation and **B.** hypermethylation direction for the 31 tumor types.



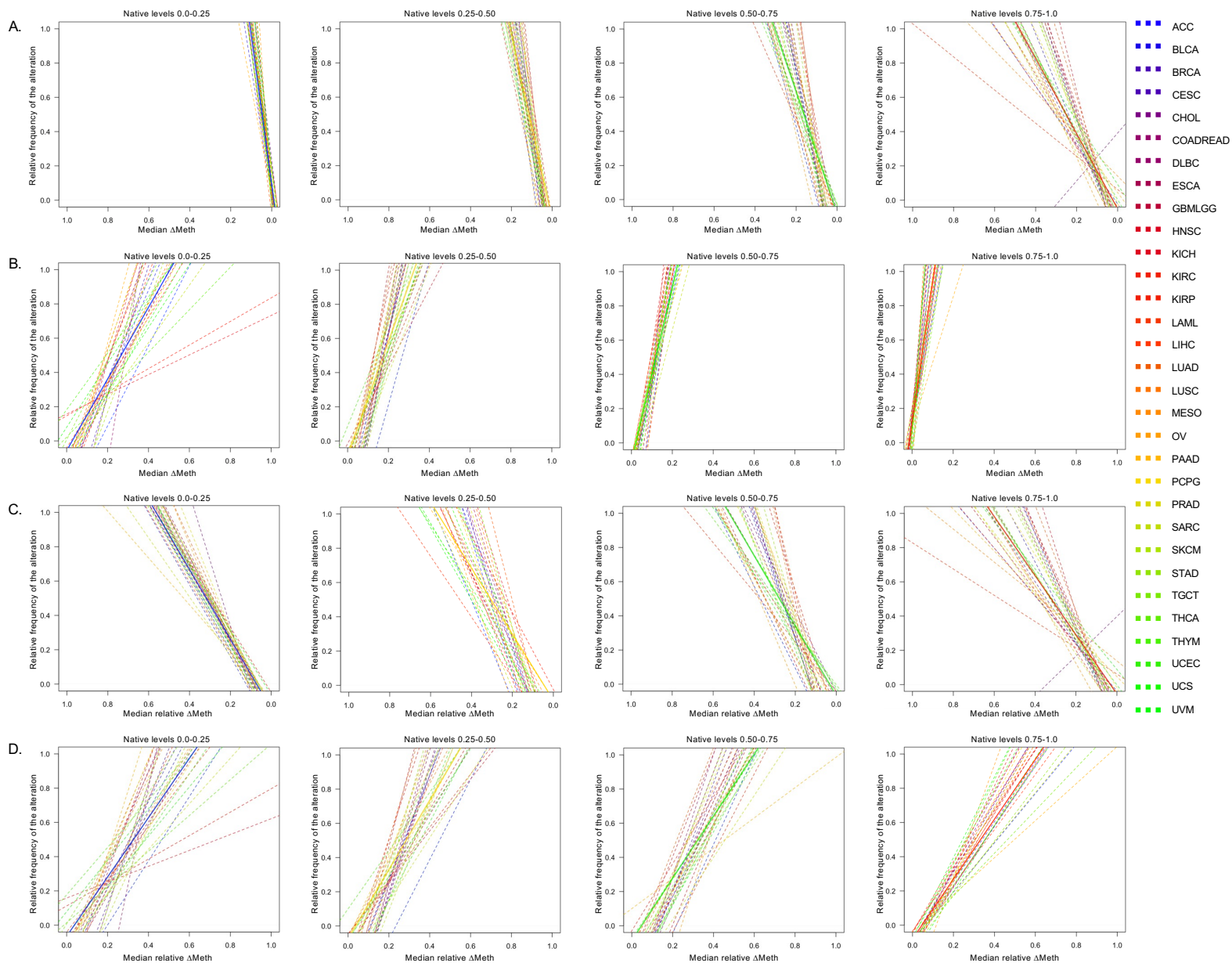
Supplemental Figure S3. Distribution of the median Δ Meth in the **A.** hypomethylation, and **B.** hypermethylation direction at different genomic regions. Distribution of the median relative Δ Meth in the **C.** hypomethylation and **D.** hypermethylation direction at different genomic regions.



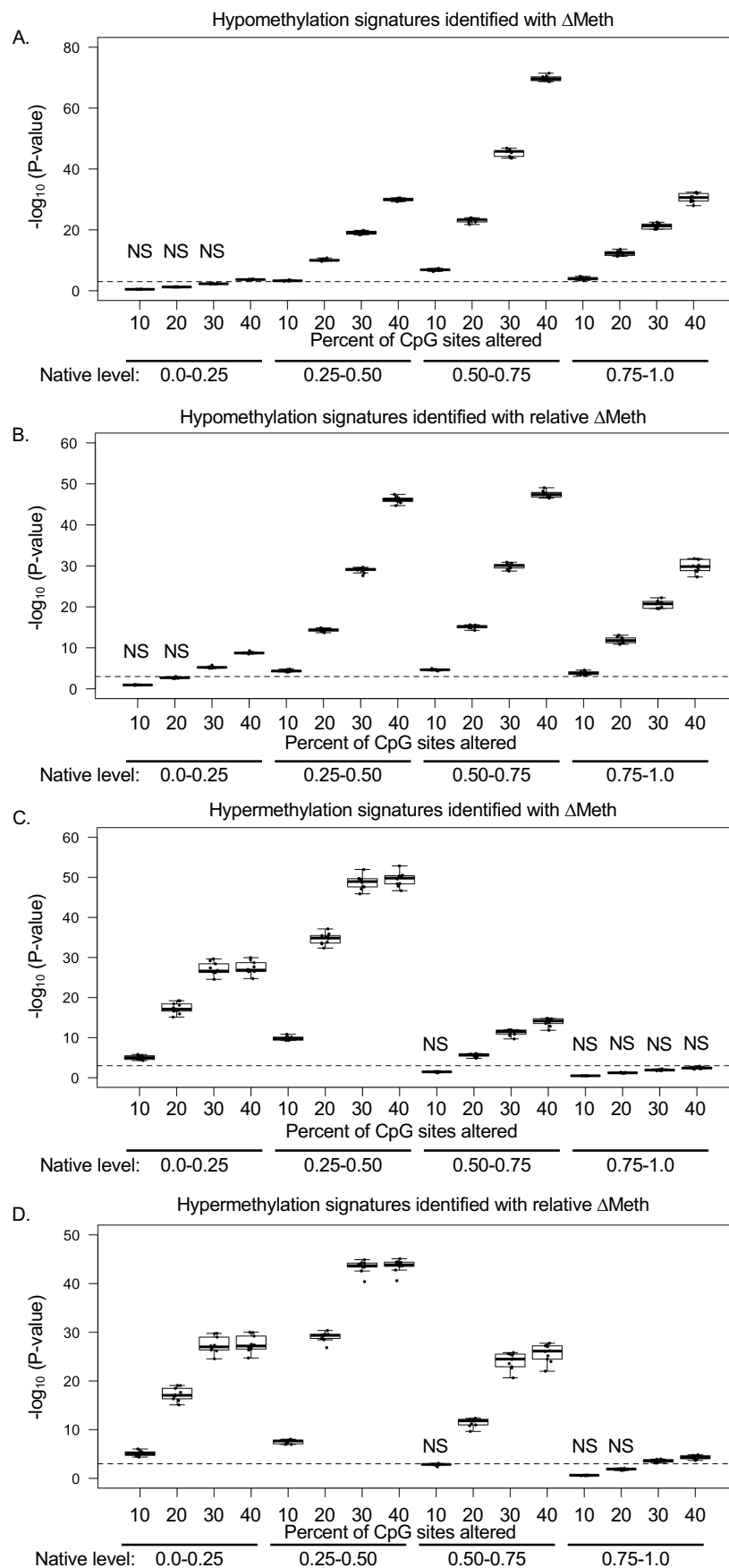
Supplemental Figure S4. Heatmap of the median relative Δ Meth of the CpG sites with varying levels of native DNA methylation in the **A.** hypomethylation and **B.** hypermethylation direction for the 31 tumor types.



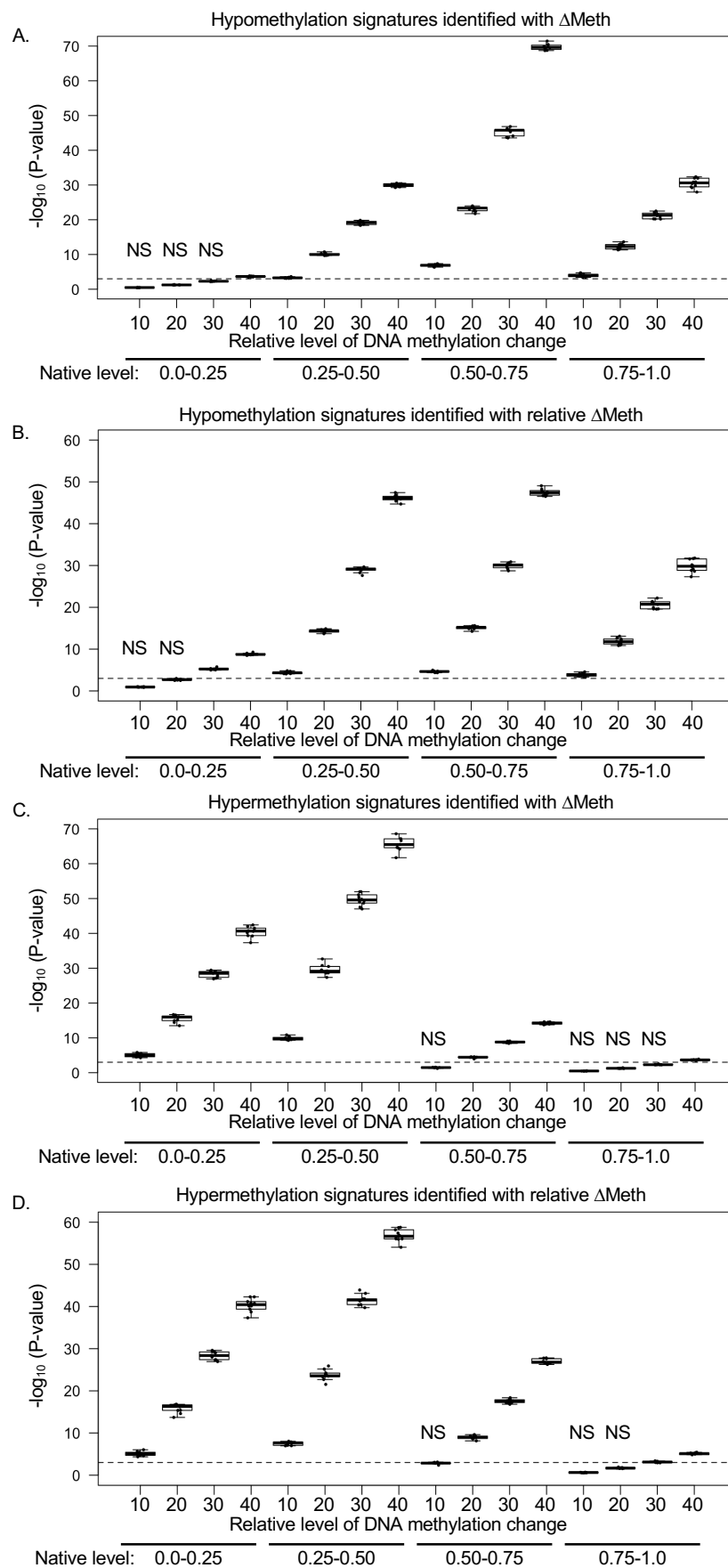
Supplemental Figure S5. Density plots of the median relative Δ Meth from the randomly generated DNA methylation dataset (N=8,551) in the **A.** hypomethylation and **B.** hypermethylation direction. Line plots showing the correlation between the proportion of cancer samples with the DNA methylation alteration and the median level of relative Δ Meth from the randomly generated data in the **C.** hypomethylation and **D.** hypermethylation direction.



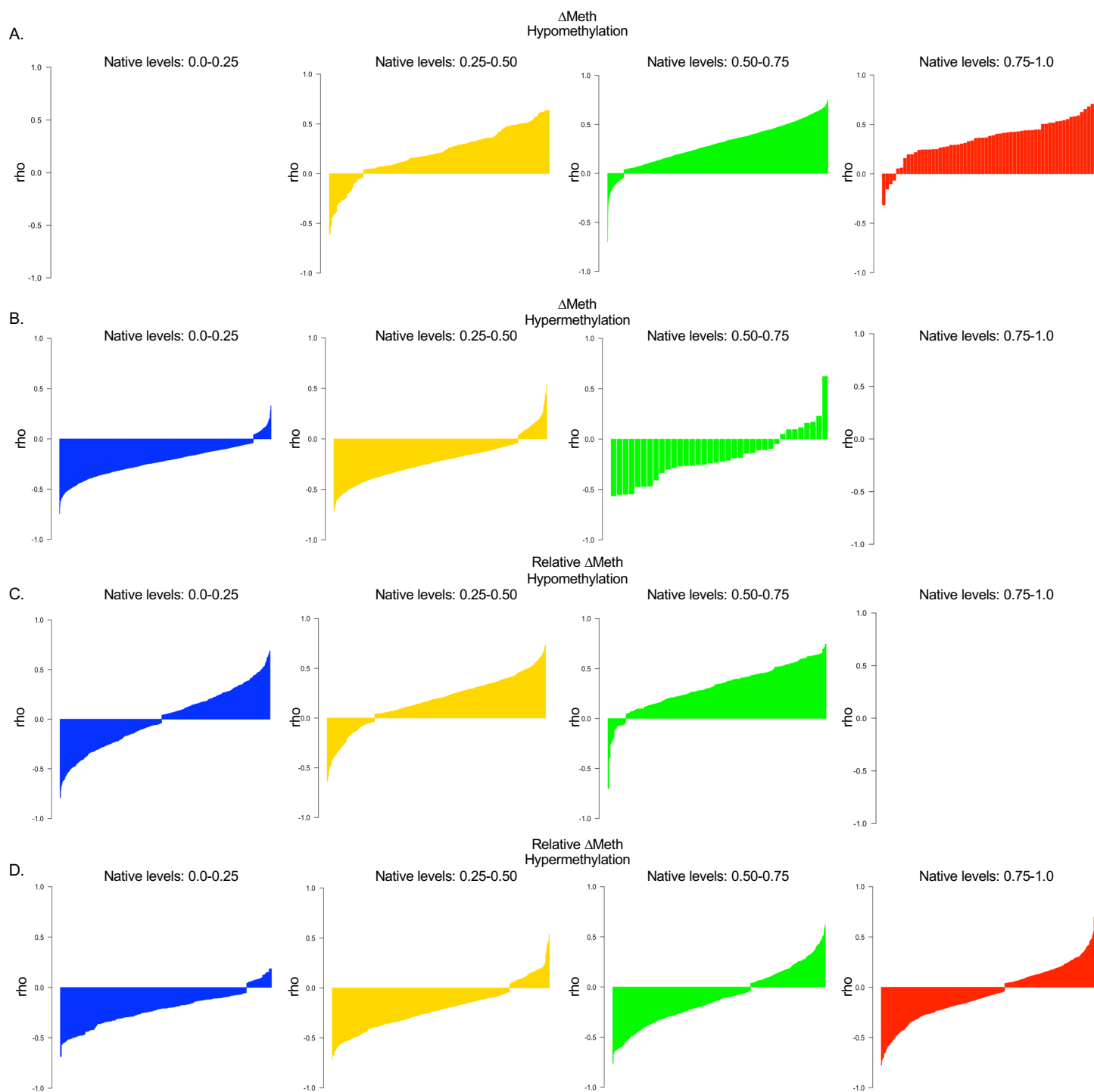
Supplemental Figure S6. Line plots showing the correlation between the proportion of cancer samples with the DNA methylation alteration and the level of median Δ Meth in the **A.** hypomethylation and **B.** hypermethylation direction and the median relative Δ Meth in the **C.** hypomethylation and **D.** hypermethylation direction. Bold lines represent the median slope.



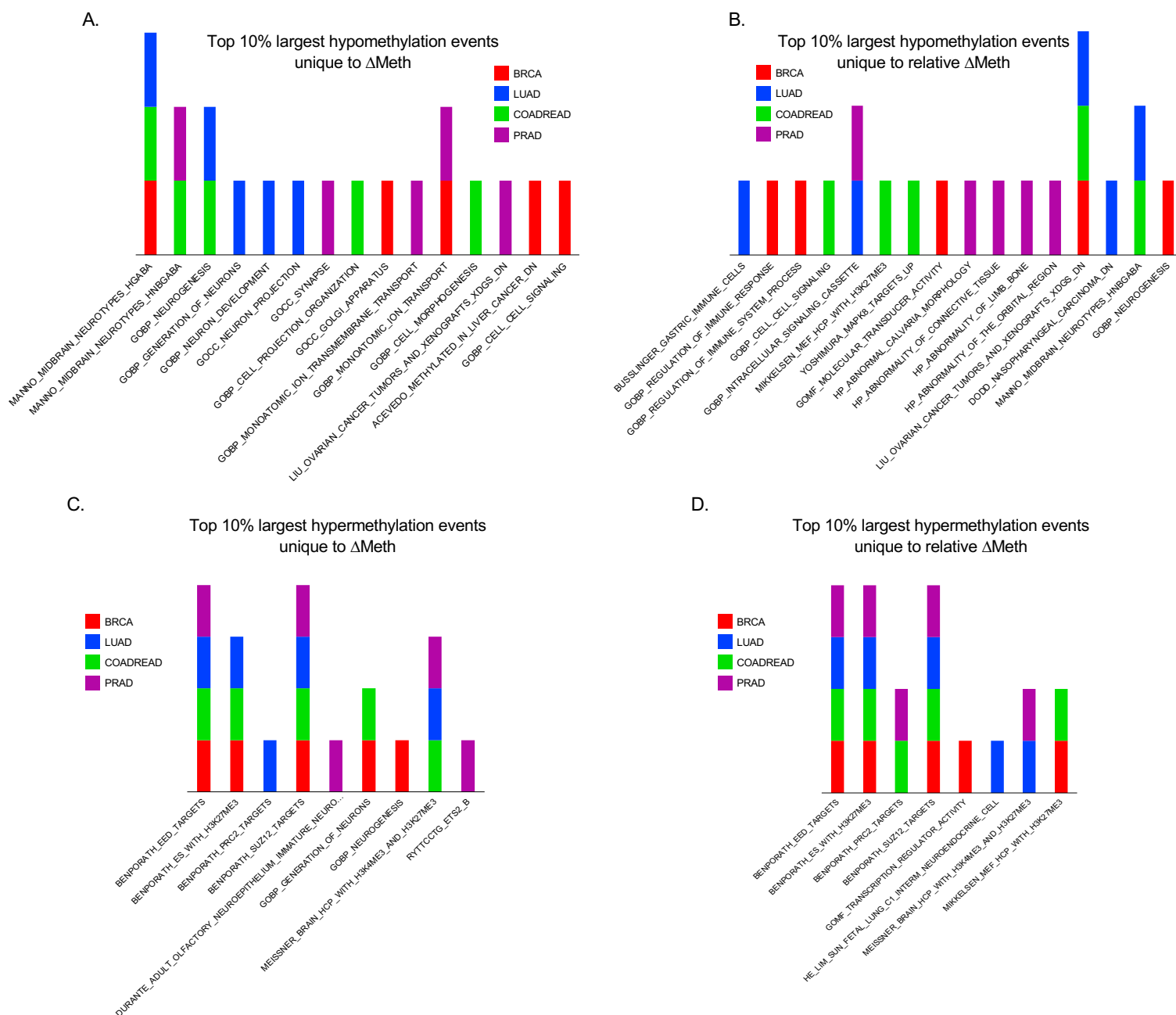
Supplemental Figure S7. Box plots show the ability of Δ Meth and relative Δ Meth to detect DNA methylation alteration signatures from a dataset of 1000 randomly selected cancer samples. To generate the signatures, we randomly selected a fraction of CpG sites, ranging between 10-40%, and altered them by a relative rate of change of 10% in the hypomethylation direction a measured the ability of **A.** Δ Meth and **B.** relative Δ Meth to detect the signatures. We also generated hypermethylation signatures and measured ability of **C.** Δ Meth and **D.** relative Δ Meth to detect the signatures. N=10 for each signature. P-value calculated from Wilcox rank sum test. Dash line at P=0.001. NS is not significant P>0.001. Center line, median; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; points, data.



Supplemental Figure S8. Box plots show the ability of Δ Meth and relative Δ Meth to detect DNA methylation alteration signatures from a dataset of 1000 randomly selected cancer samples. To generate the DNA methylation signatures, we randomly selected 10% of the CpG sites and altered them at a relative rate of change ranging between 10-40% in the hypomethylation direction and measured the ability of **A.** Δ Meth and **B.** relative Δ Meth to detect the DNA methylation signatures. We also generated hypermethylation signatures and measured ability of **C.** Δ Meth and **D.** relative Δ Meth to detect the signatures. N=10 for each signature. P-value calculated from Wilcoxon rank sum test. Dash line at P=0.001. NS is not significant P>0.001. Center line, median; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; points, data.



Supplemental Figure S9. Bar plots showing the strength and direction of correlation between DNA methylation and gene expression level identified by using ΔMeth in the **A.** hypomethylation and **B.** hypermethylation direction and by using relative ΔMeth in the **C.** hypomethylation and **D.** hypermethylation direction.



Supplemental Figure S10. Bar plots showing the top 5 most statistically significant GSEA pathway results (FDR $P < 0.05$) from the top 10% most frequent and largest alterations in genes with statistically significant correlation between DNA methylation and expression levels uniquely identified in the hypomethylation direction by **A.** Δ Meth and **B.** relative Δ Meth and in the hypermethylation direction uniquely identified by **C.** Δ Meth and **D.** relative Δ Meth.