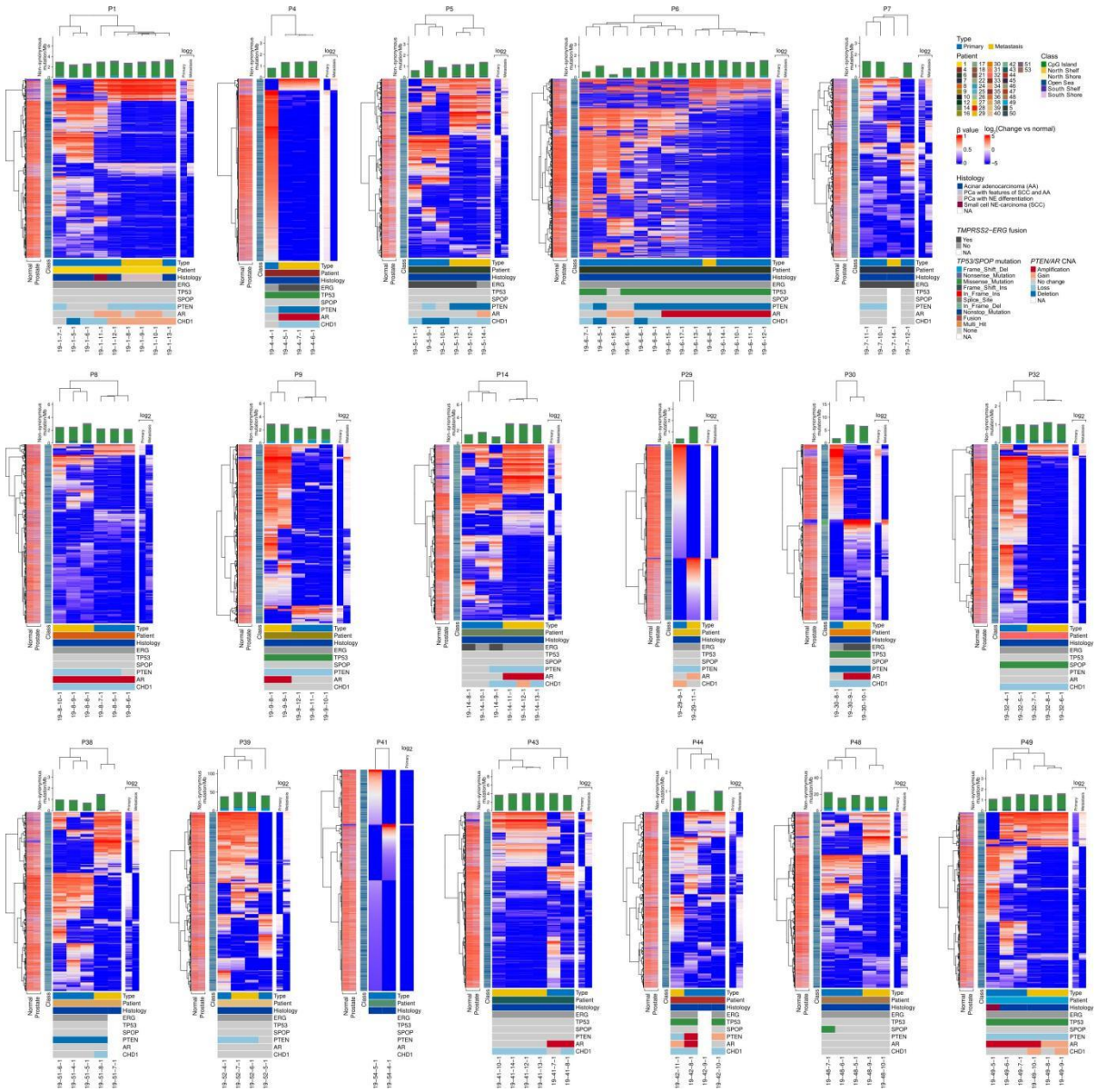
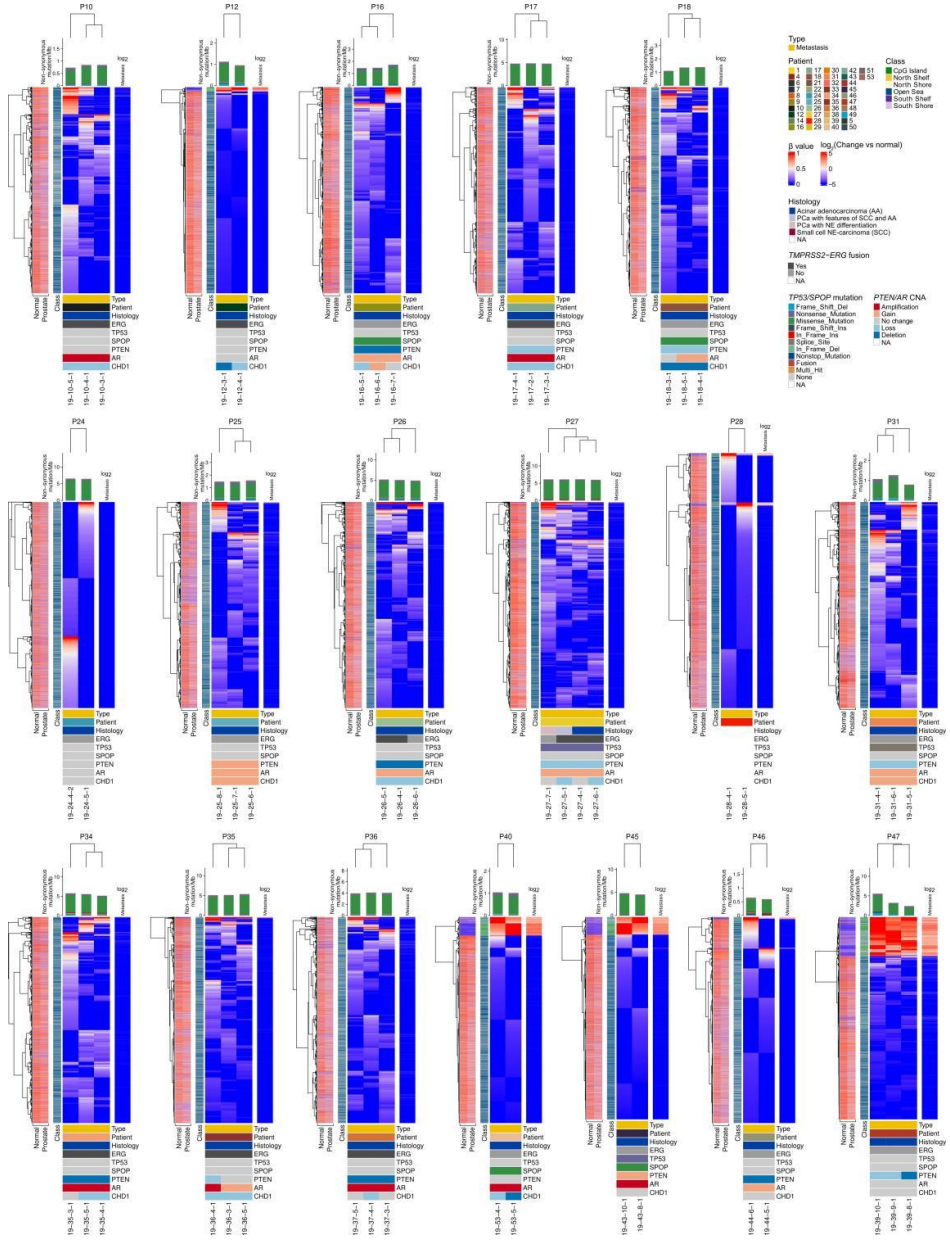
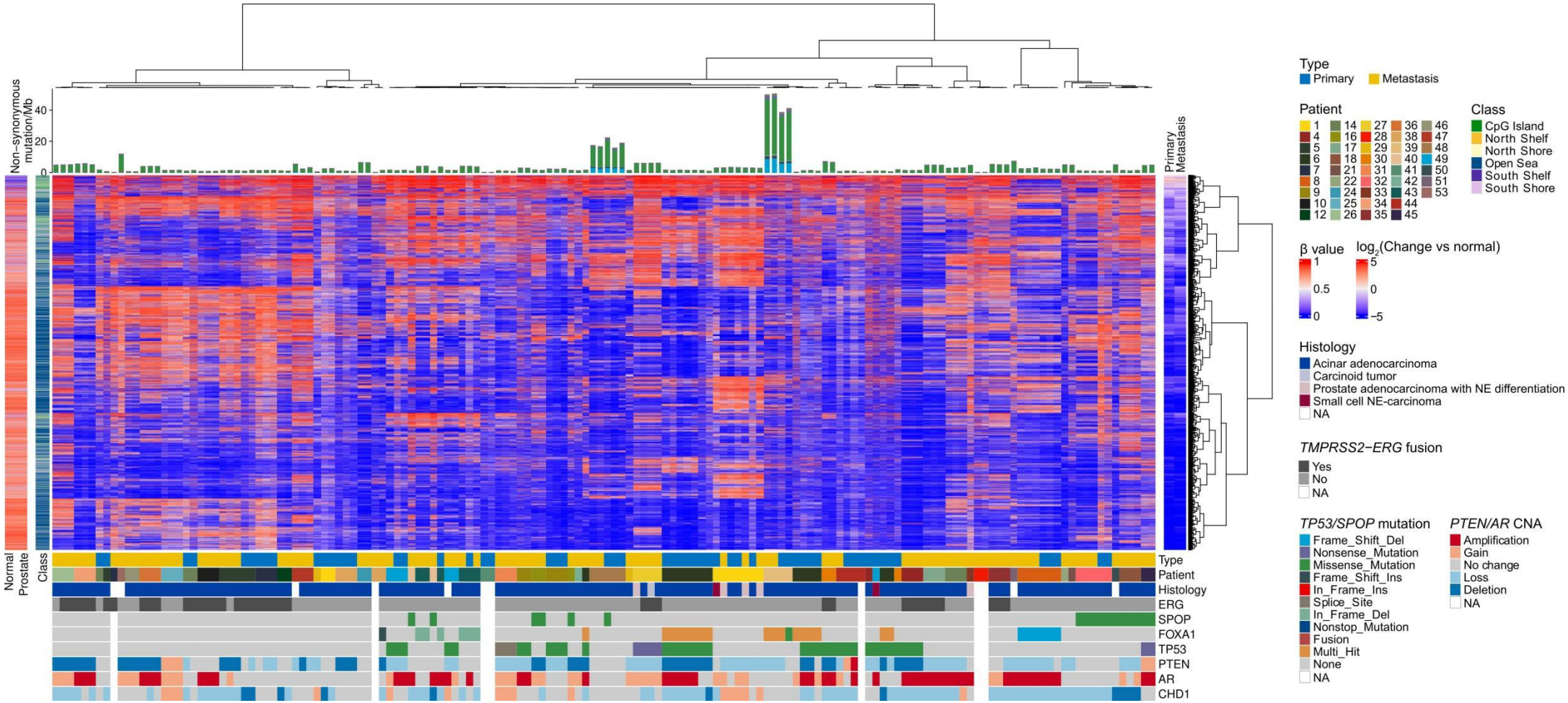
Supplementary Figs.



Supplementary Fig. S1. Most PCBM cases showed separation of primary and metastatic samples.
Samples from each patient were clustered using 1% most variably methylated CpG sites from Illumina EPIC array (8,038 sites). Heatmap shows β values for primary and metastatic samples. Class of CpG (in relation to CpG island) is shown in blue/green heatmap on left, along with methylation status of CpG sites in normal prostate tissue. Average $\log_2$ fold change in B value for primary and metastatic samples, compared to normal prostate tissue are shown on the right. Mutational burden (mutations/Mb) is shown in the barplot on top (not available for P41). Sample type (primary or metastatic), histology and genetic alterations from whole exome sequencing are annotated below.

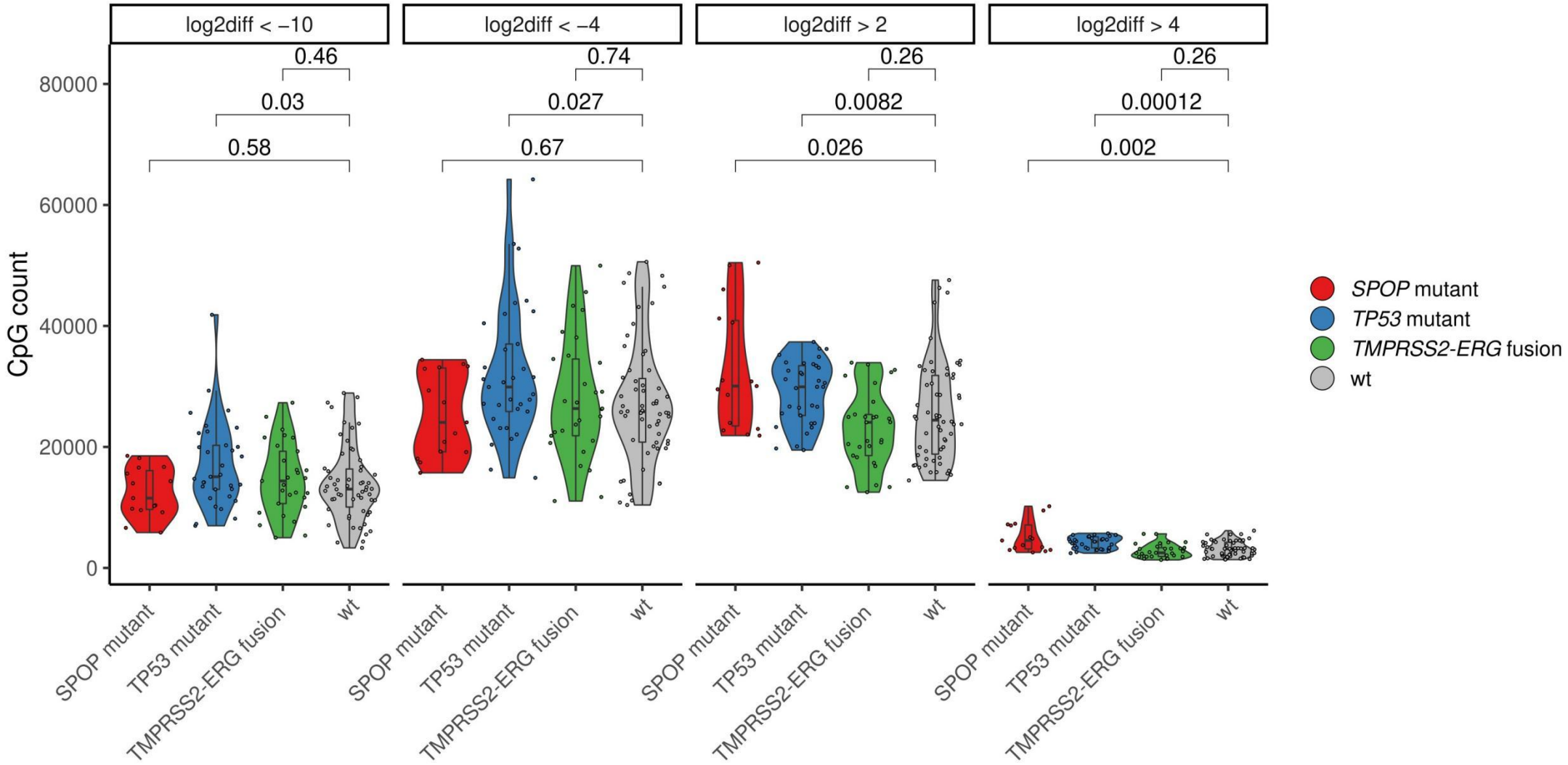


Supplementary Fig. S2. Intra-metastatic epigenetic heterogeneity in PCBM.
Unsupervised clustering of regions from metastases of 18 PCBM patients. Samples from each patient were clustered using 1% most variably methylated CpG sites from Illumina EPIC array (8,038 sites). Heatmap shows β values. Class of CpG (in relation to CpG island) is shown in blue/green heatmap on left, along with methylation status of CpG sites in normal prostate tissue. Average $\log_2$ fold change in B value for primary and metastatic samples, compared to normal prostate tissue, are shown on the right. Mutational burden (mutations/Mb) is shown in the barplot on top (not available for P28). Sample type (primary or metastatic), histology and genetic alterations from whole exome sequencing are annotated below

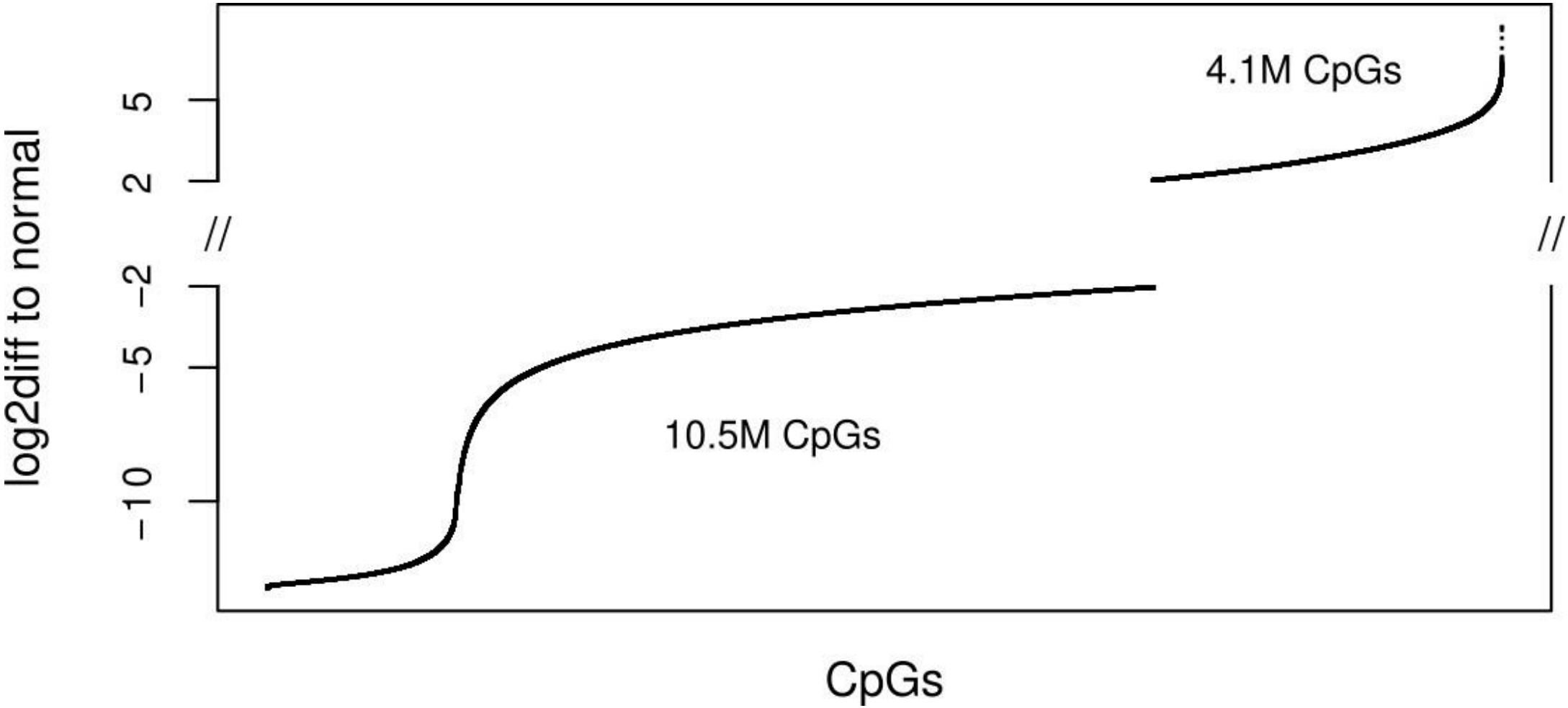


Supplementary Fig. S3. Unsupervised hierarchical clustering of all primary and metastatic samples.

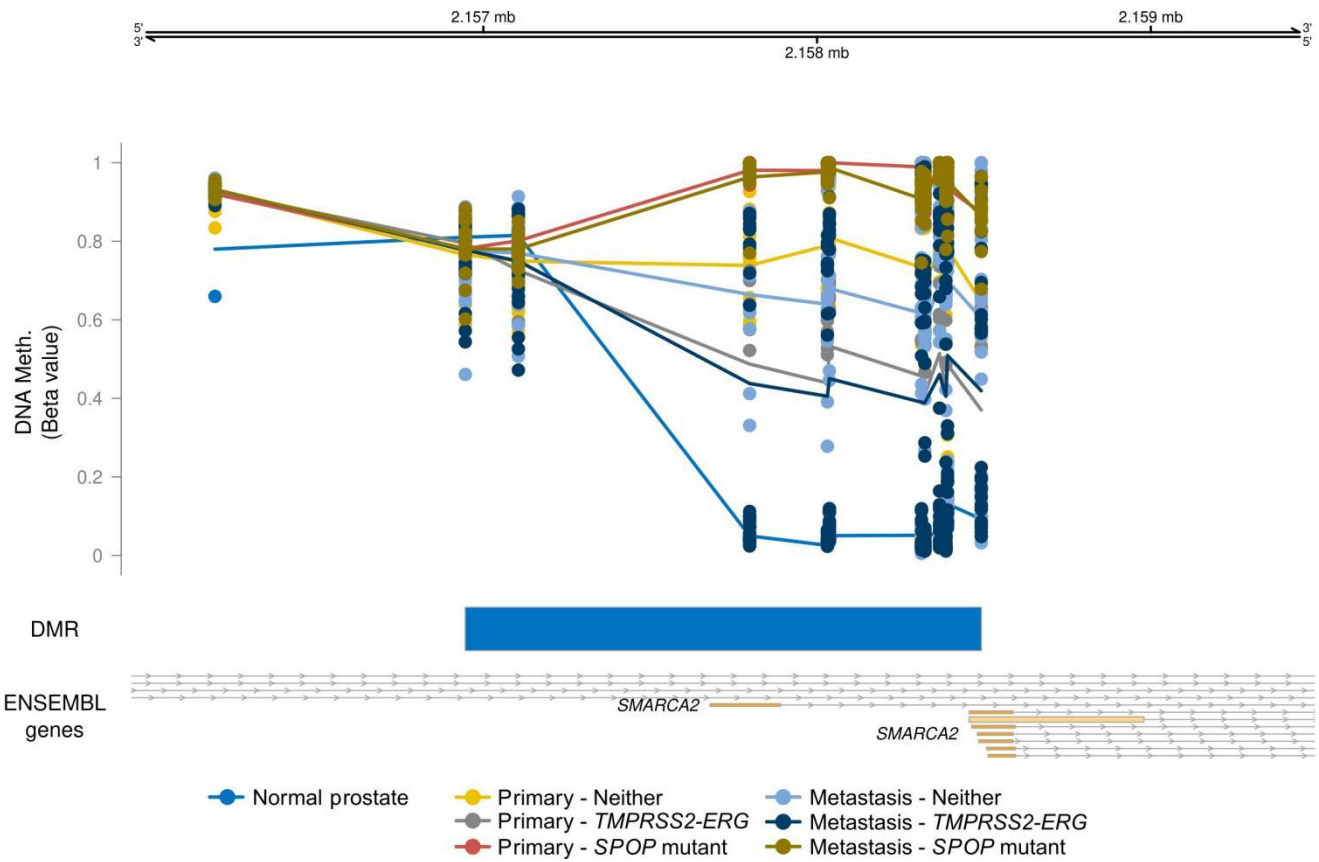
Unsupervised hierarchical consensus clustering of all primary and metastatic samples. Samples from each patient were clustered using 1% most variably methylated CpG sites from Illumina EPIC array (8,038 sites). Heatmap shows β values. Class of CpG (in relation to CpG island) is shown in blue/green heatmap on left, along with methylation status of CpG sites in normal prostate tissue. Mutational burden (mutations/Mb) is shown in the barplot on top. Average $\log_2$ fold change in B value for primary and metastatic samples, compared to normal prostate tissue, are shown on the right. Sample type (primary or metastatic), histology and genetic alterations from whole exome sequencing are annotated below.



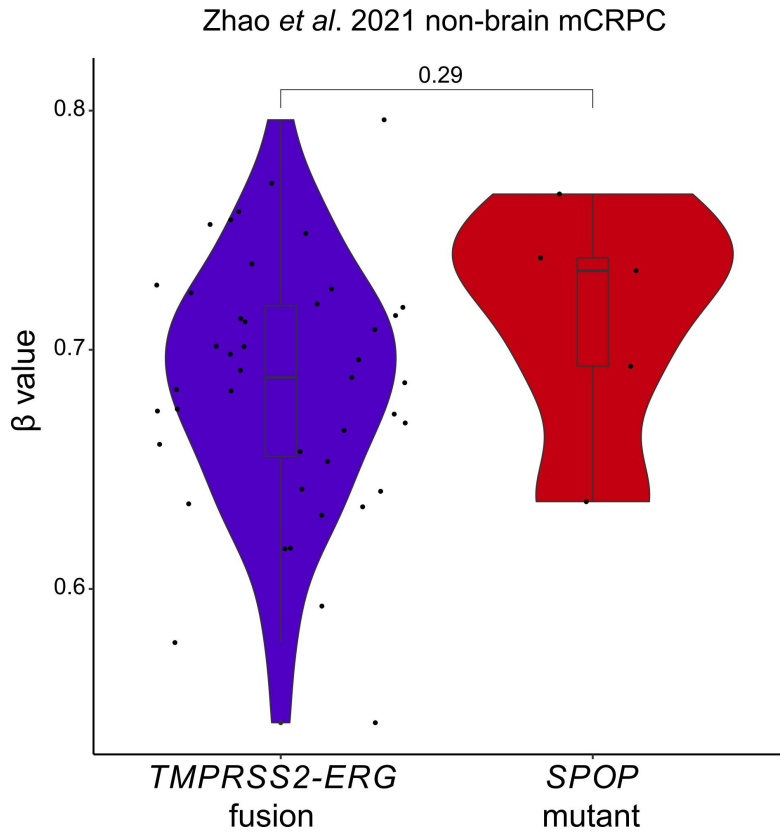
Supplementary Fig. S4. *SPOP* mutants have more hypermethylated CpGs compared to other samples.
Number of CpG sites with a $\log_2$ fold difference to the mean β value of normal prostates, below or above a given threshold (top). Wilcoxon tests.



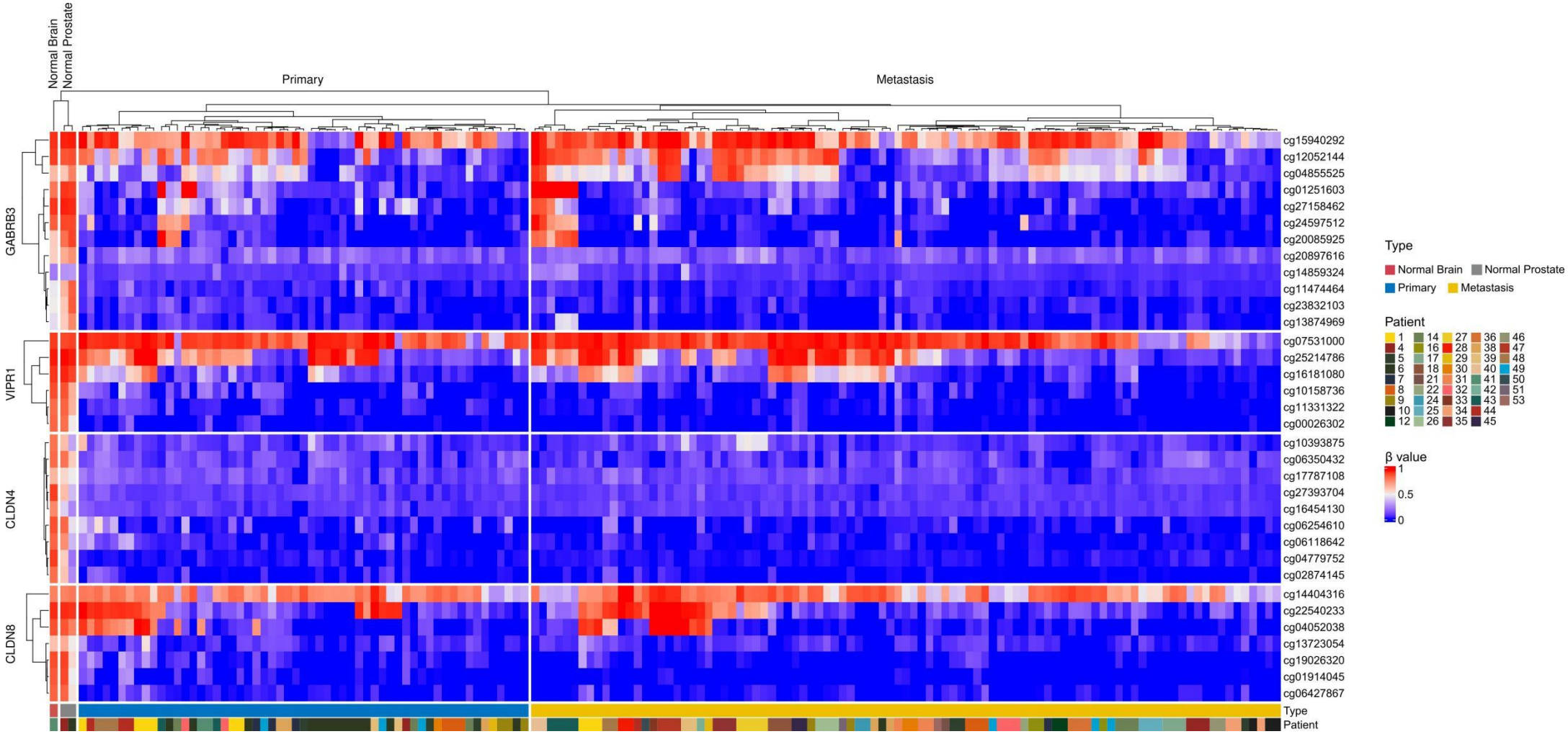
Supplementary Fig. S5. Strongly hypomethylated CpGs were more frequent than strongly hypermethylated CpGs.
Log_2 fold difference between the mean β value of all tumor samples and the mean β value of normal prostates. Showing only CpGs with log_2 fold difference below -2 and above 2. Superimposing this type of plot of all individual tumour samples results in a virtually identical plot.



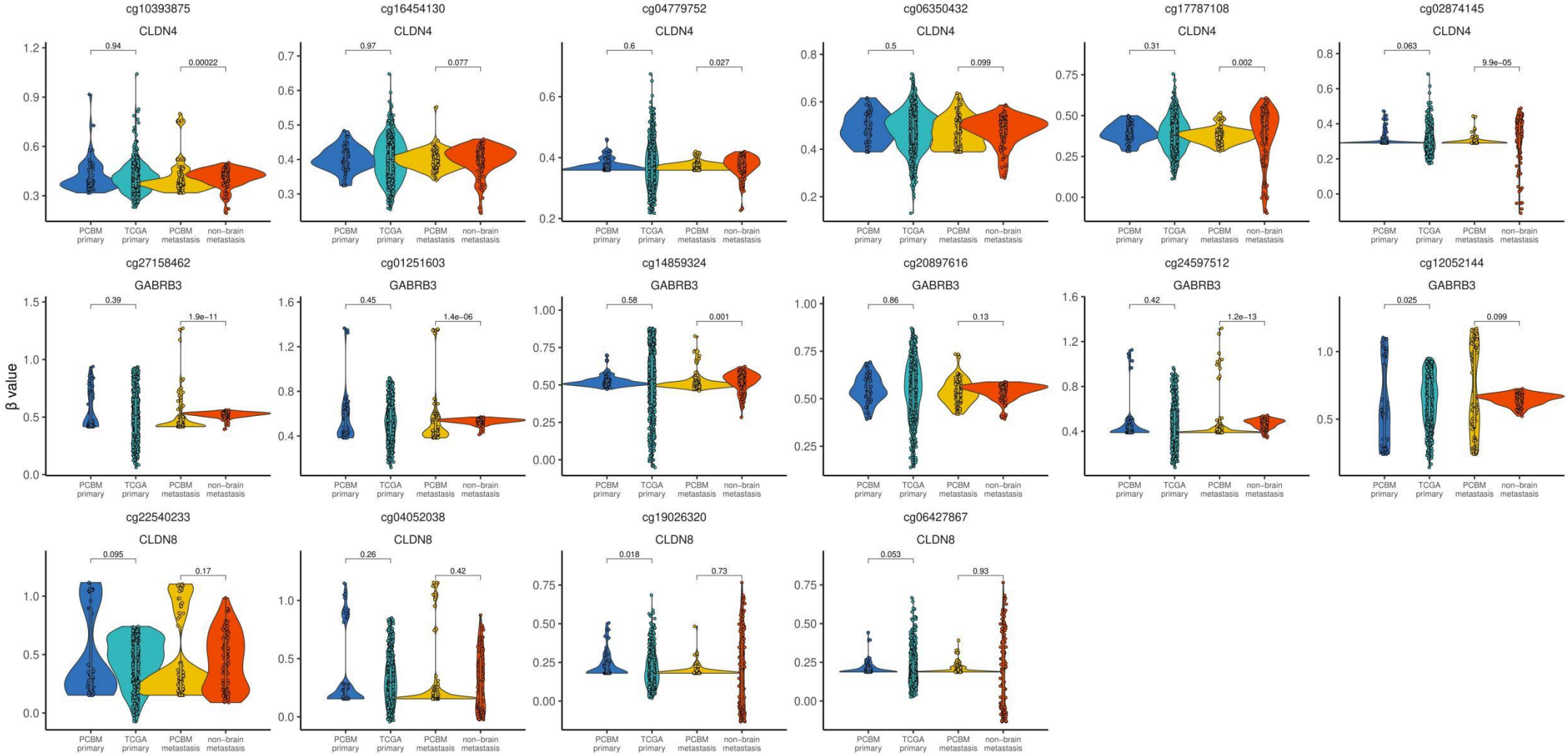
Supplementary Fig. S6. Hypermethylation at *SMARCA2* promoter.
Track plots showing methylation levels at the promoter of *SMARCA2*. Samples are stratified according to type (normal, primary or metastasis) and by mutational background (*SPOP* mutation, *TMPRSS2-ERG* fusion, or neither).



Supplementary Fig. S7. Mean methylation of CpG island-associated CpG sites in non-brain metastases from Zhao *et al.* 2021.
Samples were stratified by either *TMPRSS2-ERG* fusion or *SPOP* mutation. *P* values computed from Wilcoxon test.



Supplementary Fig. S8. Methylation of *GABRB3*, *VIPR1*, *CLDN4* and *CLDN8* promoter-associated CpG sites.
Methylation status of CpG sites falling in the DMR at the promoters of *GABRB3, VIPR1*, *CLDN4* and *CLDN8* . Heatmap shows β values. Samples and CpG sites are clustered using Ward's minimum variance method.



Supplementary Fig. S9. Methylation of promoter-associated CpG sites of *GABRB3*, *CLDN4* and *CLDN8* across cohorts.
Level of methylation at CpG sites in promoter DMRs of *GABRB3*, ***CLDN4*** **and** ***CLDN8*** in primary samples from the PCBM cohort, TCGA primary prostate cancers, metastatic samples from the PCBM cohort, and non-brain metastases from Zhao *et al.* 2021. Wicoxon test. PCBM primary n=57, TCGA primary n=502, PCBM metastasis n=95, non-brain metastasis n=100.