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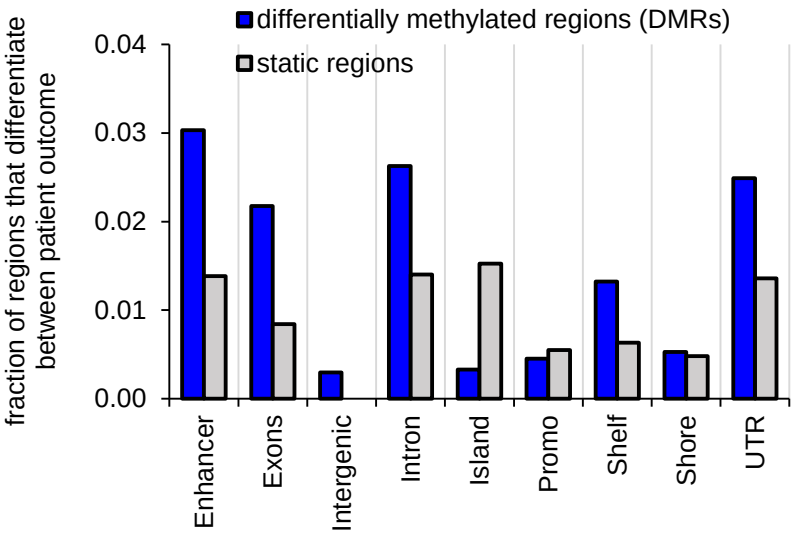

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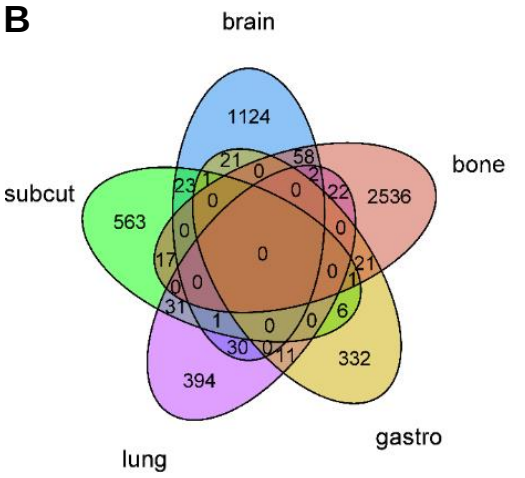

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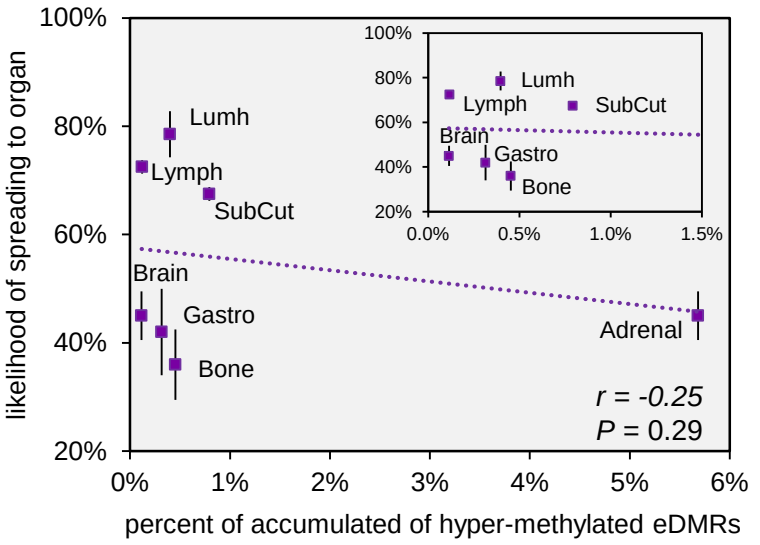

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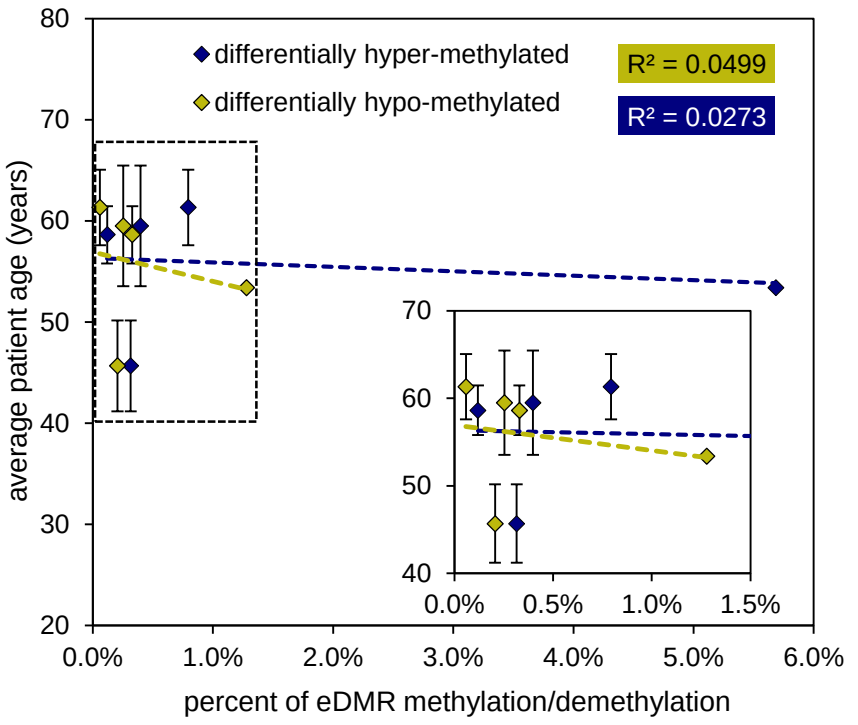

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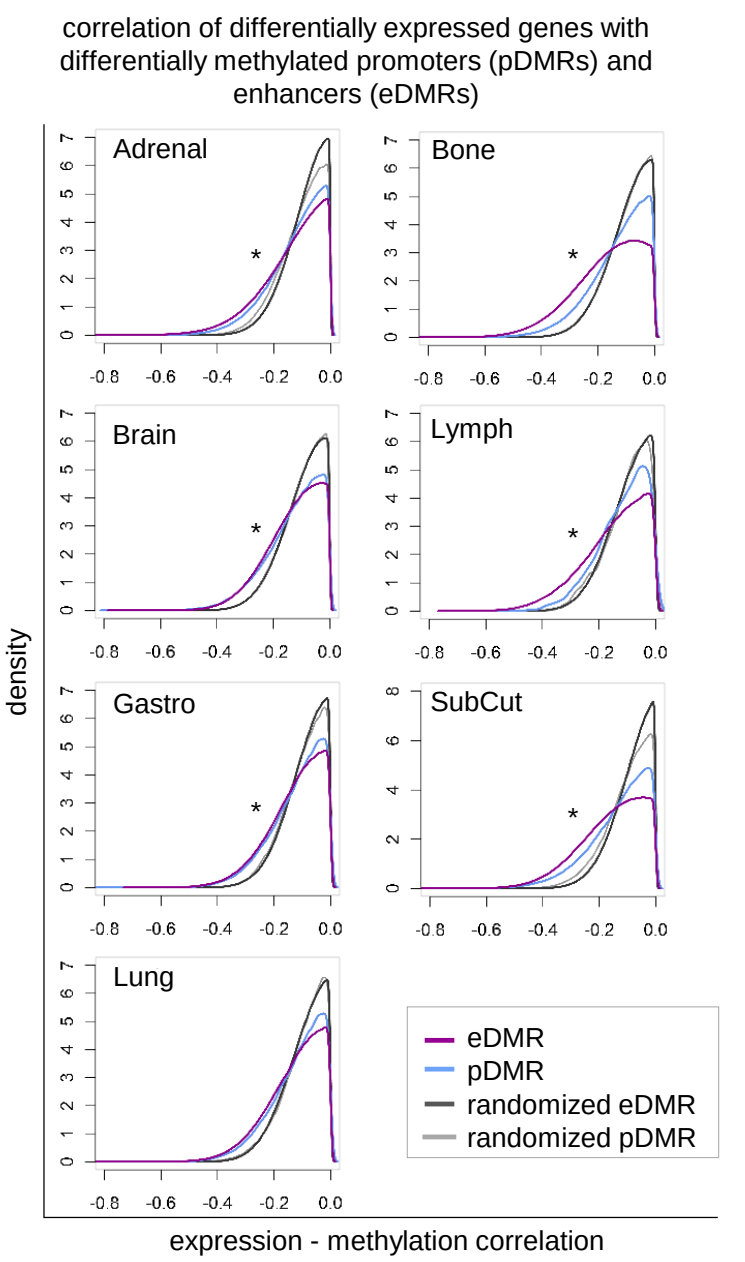

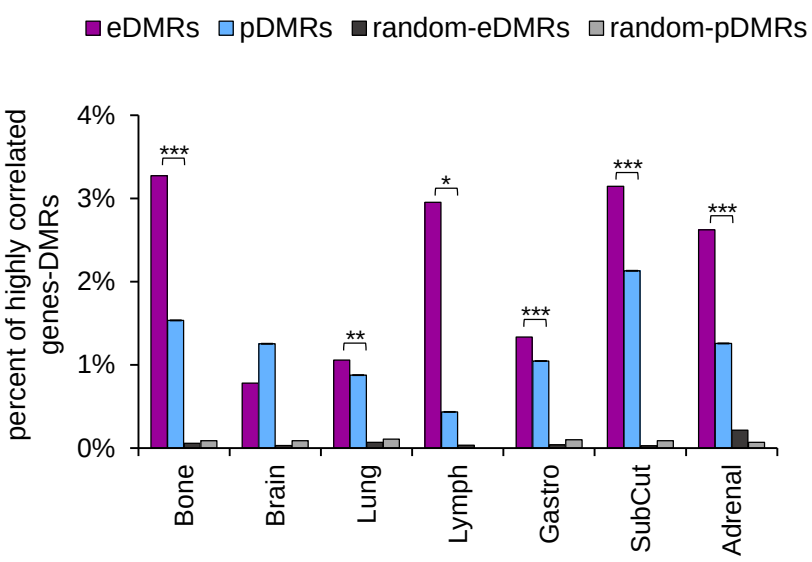

Supplemental Figure S3: Accumulation of eDMR hypomethylation correlates with likelihood of metastasis and patient outcome

Supplemental Figure S3: Accumulation of eDMR hypomethylation correlates with likelihood of metastasis

(A) EDMRs are significantly enriched with regions that are highly correlated with patient survival times, whereas, islands and promoters are depleted. Methylation patterns of DMRs (blue bars) are compared to methylation patterns of regions with no differential methylation (static regions, sized-matched samples, grey bars) in their ability to significantly differentiate between patient survival times (relative amounts are shown, y-axis). (B) Venn diagram of the number of eDMRs in five metastatic melanoma body locations shows little overlap between eDMRs from different metastatic locations (similar to Fig. 2A and Fig. 3C). (C) Likelihood of spreading to distant locations is poorly correlated with the fraction of differentially hypermethylated eDMRs (compare to hypomethylated eDMRs in Fig. 3D). Inset: Metastatic locations with less than 1.5% fraction of hypermethylated eDMRs. R-squared represents Pearson's correlations between fraction of hypermethylated eDMRs and likelihood of spreading to organ. (D) Accumulation of methylation changes at eDMRs (hypermethylation, blue; hypomethylation, yellow) is poorly correlated with patient age, shown are five metastatic melanoma locations for which data was available. Inset: Metastatic locations with less than 1.5% fraction of methylation changes. R-squared represents Pearson's correlations between fraction of hypermethylated or hypomethylated eDMRs (blue and yellow, respectively) and patients' ages. (E) Top: Probability density functions show that differentially expressed genes are more strongly correlated with eDMRs (purple curves) than with differentially methylated promoters (pDMRs, blue curves); matched patient samples were used. Correlation of gene expression with eDMR and pDMRs in randomly shuffled patients show weaker values (dark and light grey curves, respectively). Spearman's correlations are shown. Bottom: Bar plot shows the percent of highly correlated differentially expressed genes with eDMRs, pDMRs, randomly shuffled eDMRs, or randomly shuffled pDMRs (color-coding is the same as in the top plots). Significance was determined by comparing the distribution of correlations of eDMRs (purple) or pDMRs (blue) with the differentially expressed genes; using two-sample two-sided Student's t-test and was FDR corrected, *, $q<0.05$, **, $q<1e-6$, ***, $q<1e-9$.