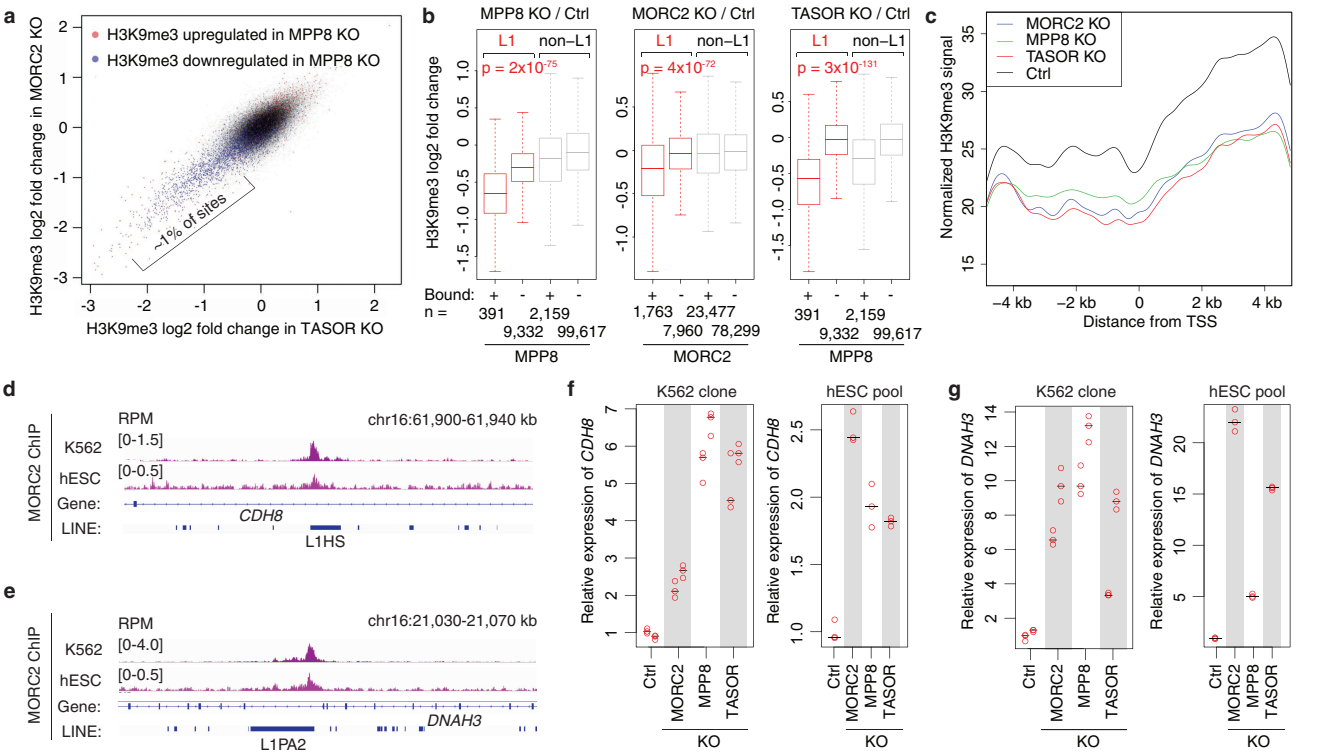

Extended Data Figure 9 | HUSH/MORC2 facilitate H3K9me3 at their L1 targets for transcription repression. a. Concordant subset (~1%) of (n = 111,499) H3K9me3 sites in the genome lose H3K9me3 signal in MORC2 KO, MPP8 KO and TASOR KO K562 clones. Two independent lines each for WT, MORC2KO, TASOR KO, MPP8 KO. Plotted is log2 fold change in H3K9me3 ChIP signal in TASOR KO relative to Ctrl (x-axis) and log2 fold change in H3K9me3 ChIP signal in MORC2 KO relative to Ctrl (y-axis). Points are color coded with blue sites having significant H3K9me3 loss in MPP8 KO, red sites significantly gaining the signal in MPP8 KO, while gray have no detectable change. Sites that significantly lose H3K9me3 signal in KO line are more likely to have corresponding loss in other KO lines. Odds ratios: 26.23 with 95% confidence intervals (CI) [23,66, 29.10] for MORC2 versus MPP8; 21.70 with 95% CI [19.75, 23.83] for TASOR versus MPP8; 122.53 with 95% CI [109.21, 137.43] for TASOR versus MORC2. P = 0 each case, two-sided Fisher's exact test. b. Genomic sites that exhibit the strongest loss of H3K9me3 in MORC2, MPP8 or TASOR KOs are preferentially L1 occupied by these factors. Boxplots of log2 fold change in H3K9me3 relative to Ctrl for MPP8 KO (left), MORC2 KO (center) and TASOR KO (right). Box plots show median and interquartile range (IQR), whiskers are 1.5× IQR. MPP8 and MORC2 bound L1s show significant loss of H3K9me3 (p-values, two-sided Mann-Whitney-Wilcoxon test). c. Averaged distribution of H3K9me3 ChIP-seq signals in Ctrl and KO K562 clones over the host genes that contain the MORC2-targeted intronic full-length L1s, centered on the transcription start site (TSS) of the host genes. d. Genome browser showing MORC2 binding at the intronic full-length L1Hs within *CDH8* in both K562 and hESCs. Experiment was repeated once with similar results. e. Genome browser showing MORC2 binding at the intronic full-length L1PA2 within *DNAH3* in both K562 and hESCs. Experiment was repeated once with similar results. f. Depletion of MORC2/HUSH increases the expression of *CDH8* in both K562 (n = 2 biological replicates x 3 technical replicates) and hESCs (n = 3 technical replicates), as measured by RT-qPCR assay. The *CDH8* expression level was normalized to beta-actin mRNA. All samples were then normalized to Ctrl sample. Center value as median. g. Depletion of MORC2/HUSH increases the expression of *DNAH3* in both K562 (n = 2 biological replicates x 3 technical replicates) and hESCs (n = 3 technical replicates), as measured by RT-qPCR assay. The *DNAH3* expression level was normalized to beta-actin mRNA. All samples were then normalized to Ctrl sample. Center value as median.

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