

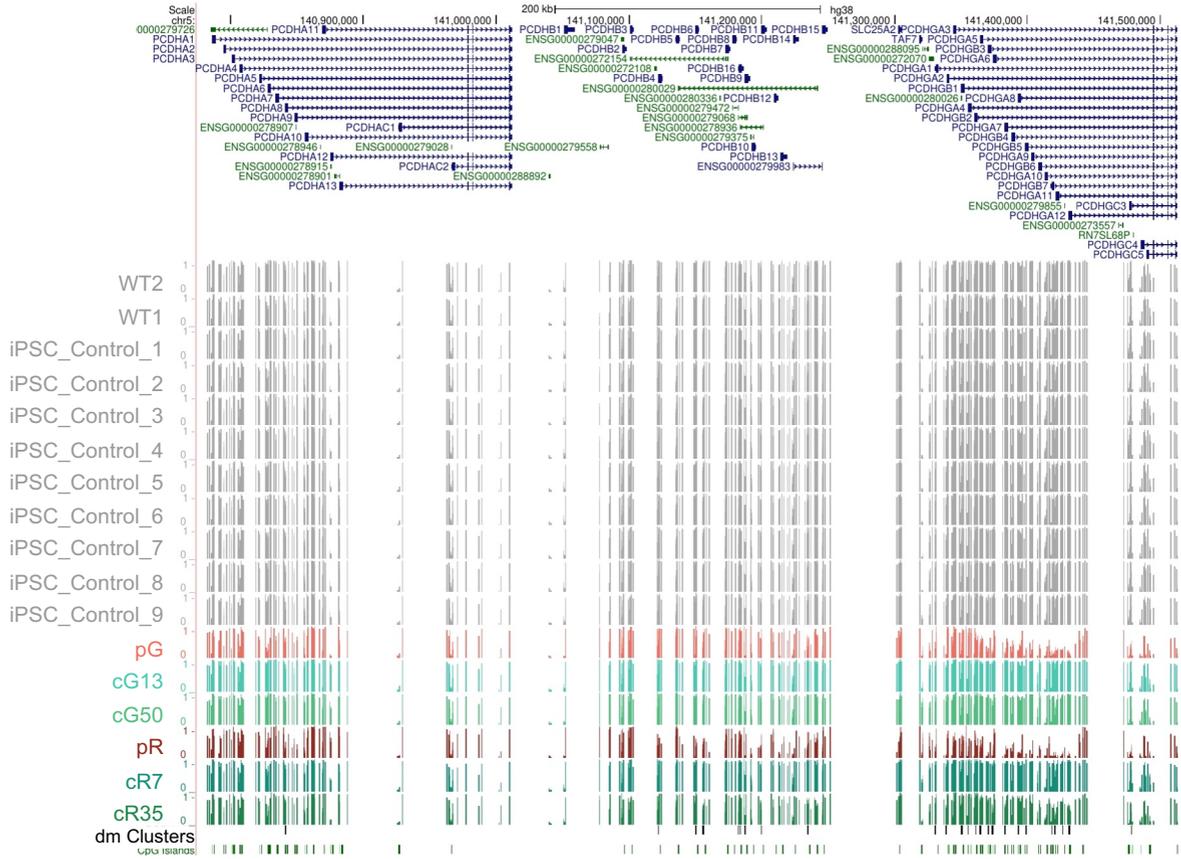
Supplementary Figure 1

A, Scatter plots show the methylation profiles of ICF1 iPSCs (pG and pR) and respective CRISPR/Cas9 corrected iPSCs (cG13, cG50 and cR7 and cR35) (y-axis) compared to median β_{ave} -value of controls iPSCs (n=11) (x-axis). Each dot corresponds to a 500bp bin (n=34,048). Grey dots account for non-differentially methylated 500bp bins. Differentially methylated (dm) 500bp bins are represented in colored dots (pG, n=940; pR, n=1285). The color filled circles (n=767) represent the dm-500bp bins that are shared between both pG and pR, while unfilled circles are affected in either pG (n=173) or pR (n=518) iPSCs. **B**, Pie charts represent the proportion of differentially methylated 500bp bins (dm-500bp bins) in ICF1 iPSCs (pG, n=940, top panel; pR, n=1285, bottom panel) and ICF1 corrected 500bp bins in cG13/cG50 and cR7/cR35, respectively. **C**, Upset plot shows the number of 500bp bins which are differentially methylated in ICF1 iPSCs and their methylation recovery status in cG13/cG50/cR7/cR35. Black and grey dots represent presence or absence of differentially methylated 500bp bins in the corresponding iPSCs, respectively. The red outline highlights the 500bp bins (440) where the methylation defect is present (black dot) in both patient iPSCs and rescued in all corrected iPSCs (grey dots). 424 and 134 500bp bins were differentially methylated specifically in pR and pG, respectively. Black lines identify bins that are affected across the corresponding iPSCs.

A

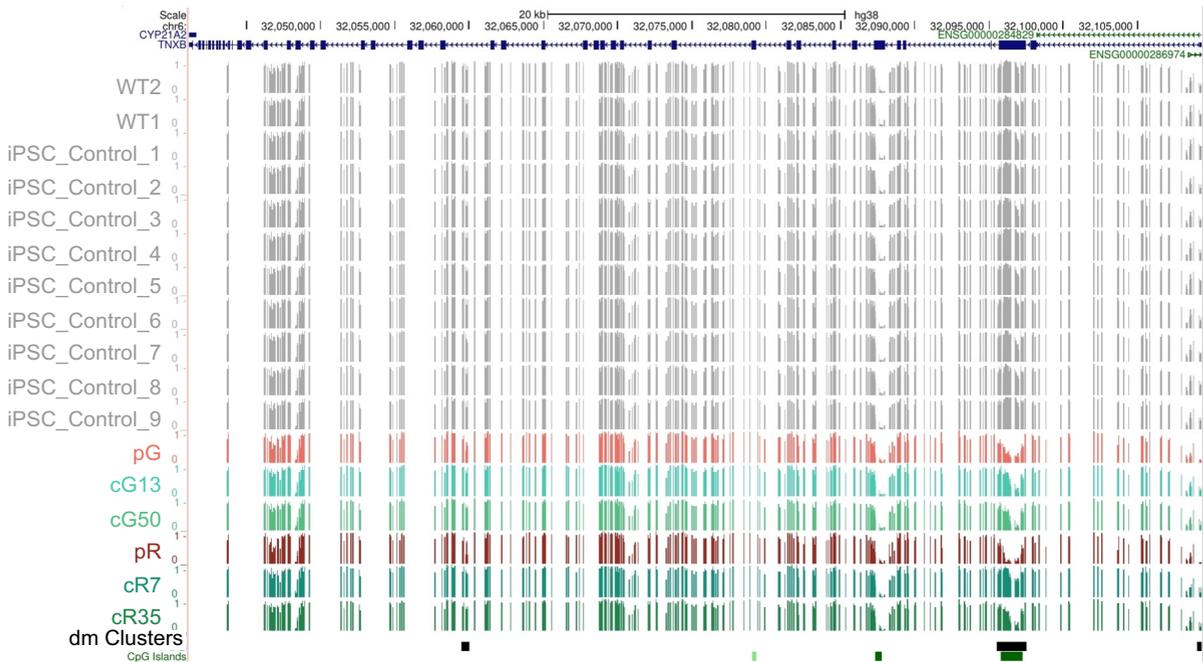
PCDH gene cluster

chr5:140,775,222-141,513,368

**B**

TNXB locus

chr6:32,039,982-32,111,007



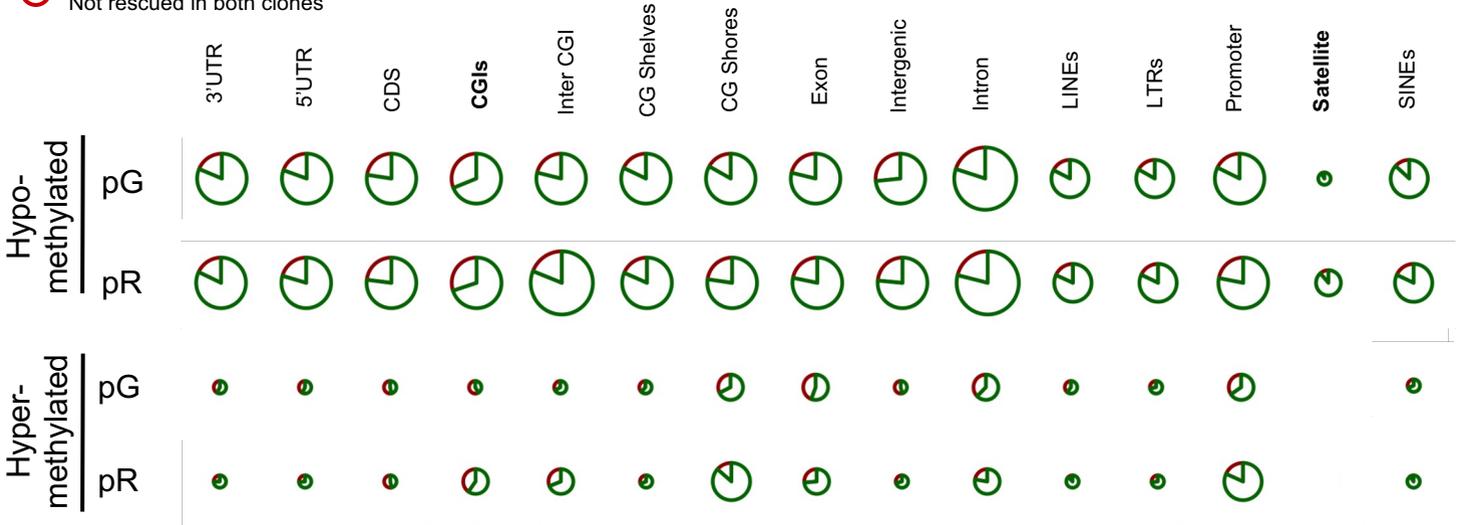
Supplementary Figure 2

A, UCSC snapshot depicts the methylation coverage of iPSC controls, ICF1 iPSCs and their corrected clones as β -values at *PCDHA*, *PCDHB* and *PCDHG* gene clusters. The locus is known to lose methylation in ICF1 syndrome [24,27] and to recover normal methylation levels at several CpGs upon DNMT3B correction by CRISPR/Cas9. **B**, UCSC snapshot of *TNXB* gene shows DNA hypomethylation that is only partially restored in corrected iPSC clones. Differentially methylated 500bp bins and CpG Islands are represented by color blocks below the tracks. Differentially methylated (dm) Clusters are shown at the bottom of UCSC tracks.

Proportion of CpGs

○ Rescued upon *DNMT3B* gene correction in both corrected clones
○ Not rescued in both clones

○ <100
 ○ 100-500
 ○ 500-1000
 ○ 1000-10000
 ○ >100000
 Number of CpGs



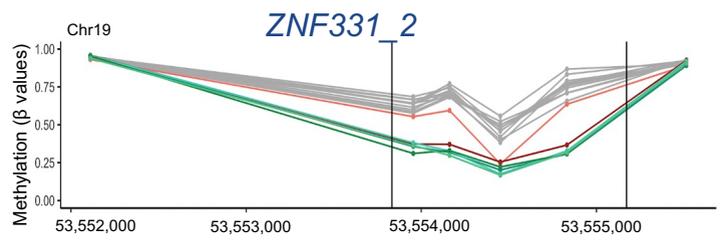
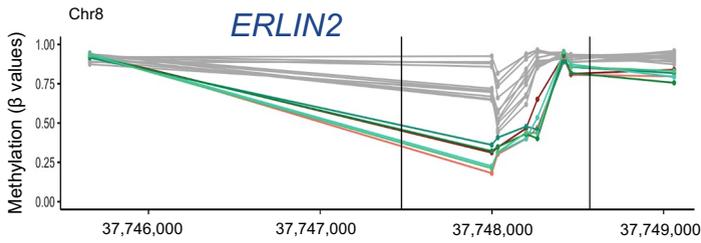
Supplementary Figure 3

Pie charts depict the proportion of differentially methylated CpGs in pG and pR iPSCs annotated to various genomic elements. The outline of the pie chart represents CpGs remaining hypo- or hypermethylated (red arc) following DNMT3B correction in at least one clone, or that are rescued in both corrected clones (green arc). The size of the pie represents the number of CpG analyzed in each of the genomic elements. CGIs and Satellites are in bold as they show the least and the highest percentage of methylation recovery upon correction, respectively. No hypermethylated satellite sequences have been found in ICF1 iPSCs.

● Controls
 ● pG
 ● pR
 ● cR7
 ● cR35
 ● cG13
 ● cG50

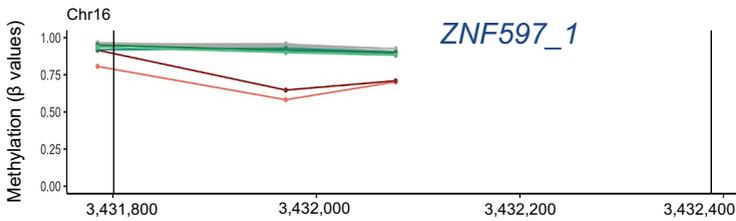
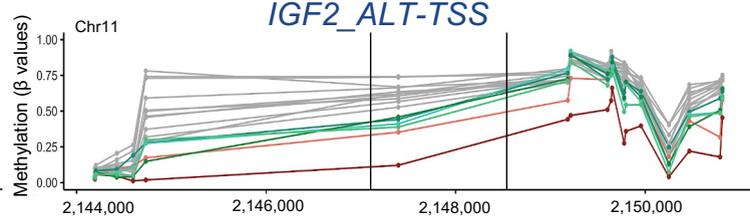
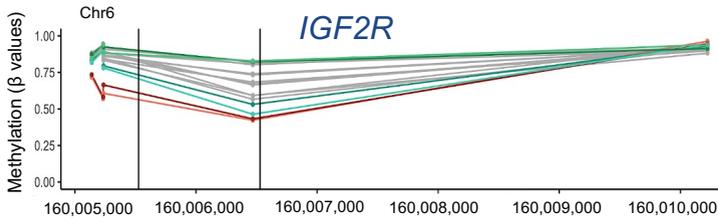
Hypomethylated imprinted DMRs in both pG and pR with non significant alterations in one of the ICF1 iPSCs (>=3 CpGs inside DMRs)

A



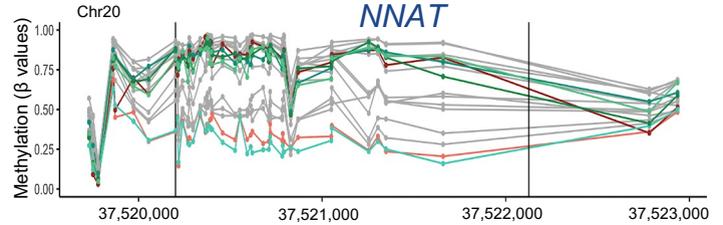
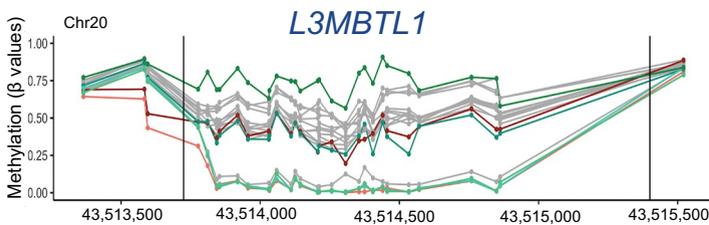
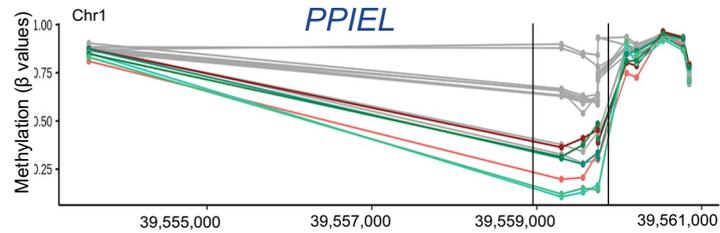
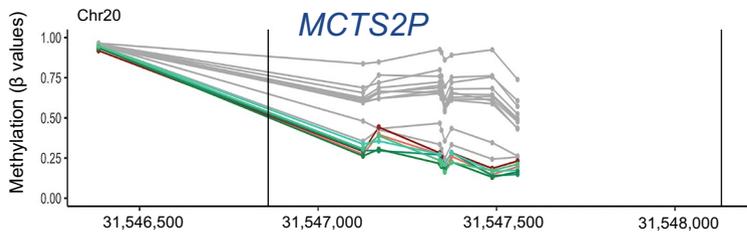
B

Hypomethylated imprinted DMRs in both pG and pR (<3 CpGs inside DMRs)



C

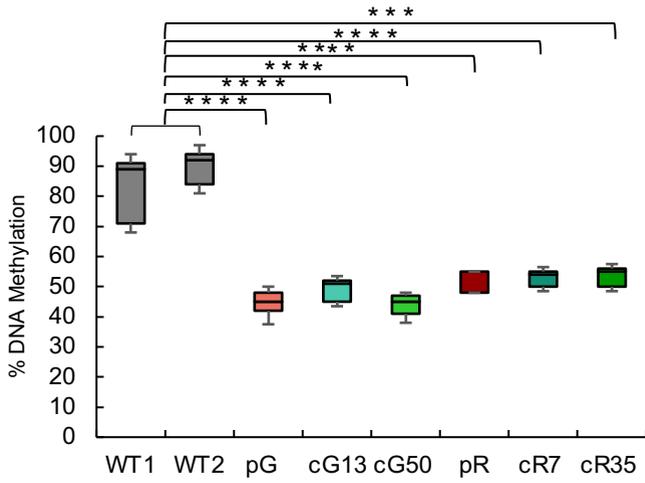
Variably methylated imprinted DMRs in control iPSCs (>=3 CpGs inside DMRs)



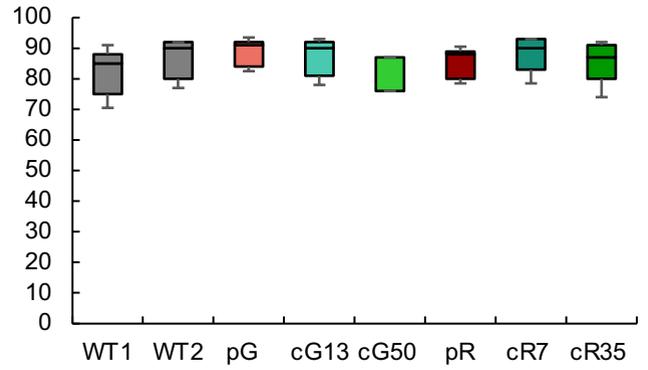
Supplementary Figure 4

Line charts depict DNA methylation profiles at the hypomethylated imprinted loci in ICF1 iPSCs, corrected iPSC lines and controls (n=11) shown in Figure 2A. The charts present the imprinted DMRs hypomethylated in both pG and pR (≥ 3 CpGs inside DMRs) with insignificant alterations in one of the ICF1 iPSCs (**A**), those hypomethylated in both pG and pR but showing less than 3 CpGs inside a DMRs (**B**), and those variably methylated among control iPSCs (≥ 3 CpGs inside a DMRs) (**C**). Dots on the line show the position of the CpGs. Two black lines within the plot represent the span of the iDMR. The x-axis represents genomic coordinates in and around the iDMRs, while the y-axis shows methylation levels (β -values).

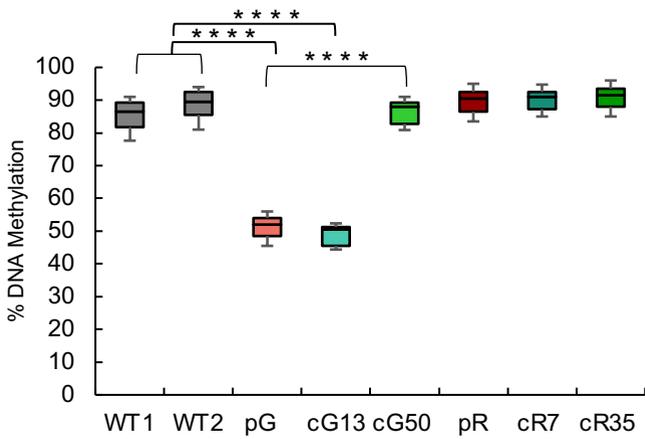
H19/IGF2:IG-DMR



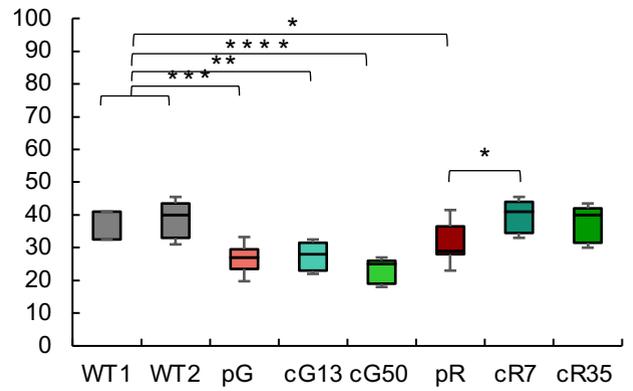
RB1:Int2-DMR



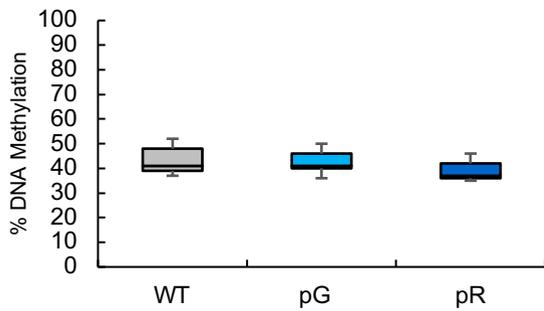
MEG3:TSS-DMR



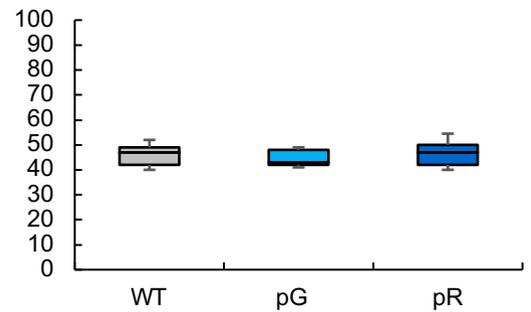
NDN:TSS-DMR



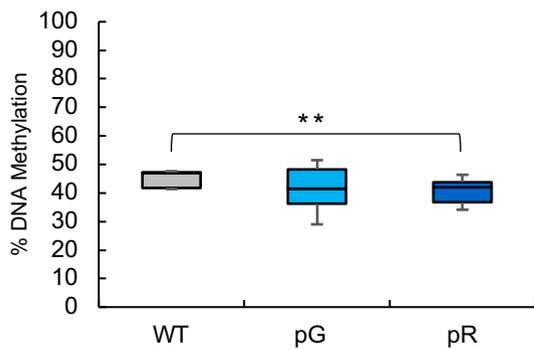
H19/IGF2:IG-DMR



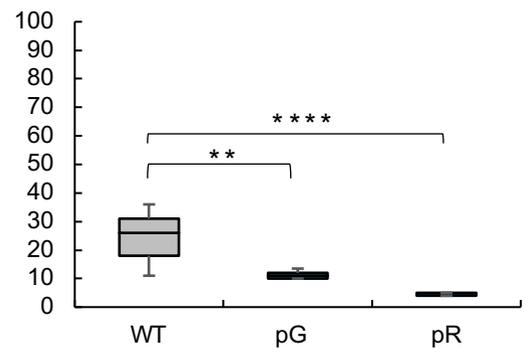
RB1:Int2-DMR



MEG3:TSS-DMR

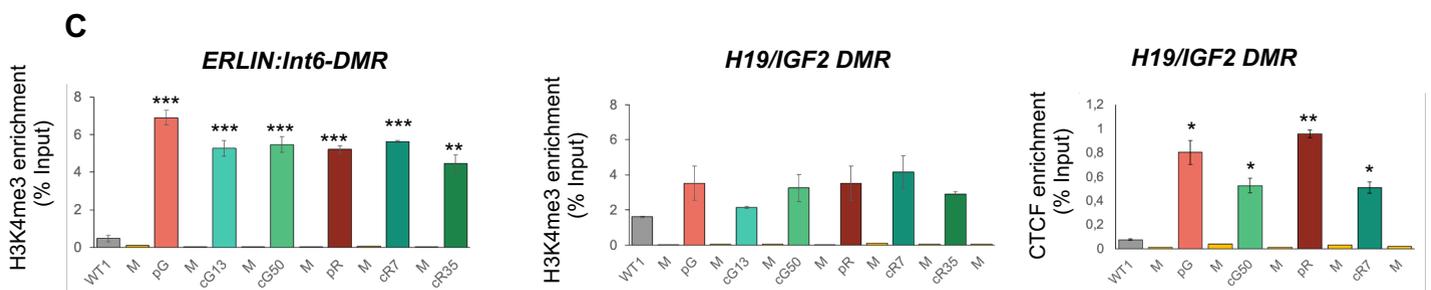
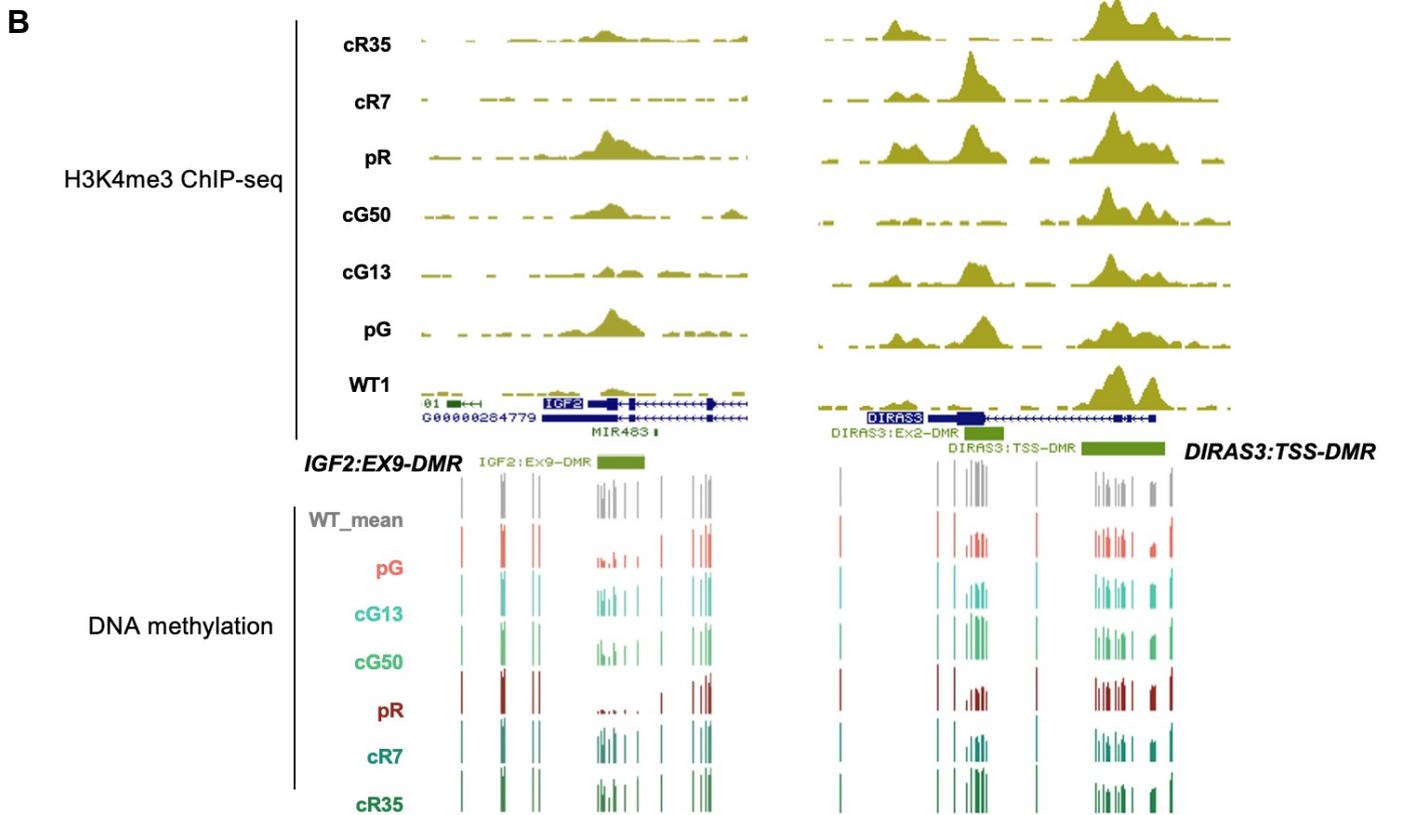
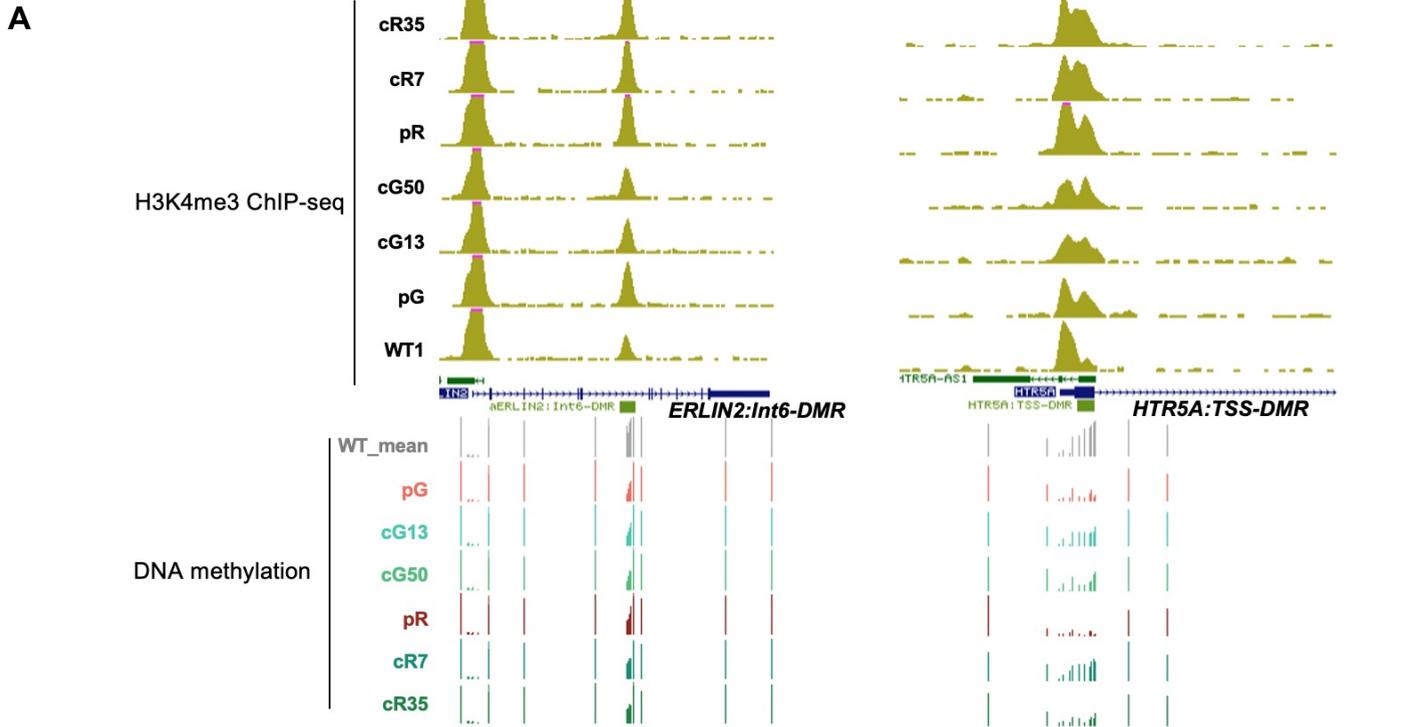


NDN:TSS-DMR



Supplementary Figure 5

Boxplot showing DNA methylation analysis of four imprinted DMRs in WT, patient and corrected iPSCs (upper panels) and in patient pR and pG parental fibroblasts (lower panels), as measured by bisulfite pyrosequencing. *P* values have been calculated by two-tailed Student's t test (** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).



Supplementary Figure 6

Genome browser view of the *IGF2:Ex9* and *DIRAS3:Ex2* (**A**) and *HTR5A* and *ERLIN2* (**B**) imprinted DMRs (green bars below the GENCODE V43 gene tracks). The coverage tracks from the top to the bottom display the H3K4me3 enrichment levels (light green) obtained by previously published ChIP-Seq data [24] and the methylation level shown as β -values for all iPSCs (control, ICF1, and corrected iPSC clones) obtained in this study.

C, ChIP-qPCR measuring H3K4me3 levels at *ERLIN:Int6-DMR* and *H19/IGF2 DMR* (left and middle panels) and CTCF binding level (right panel) in WT, ICF1 and corrected iPSCs. Amplicon enrichment in immunoprecipitated and mock samples (M, orange bars) is expressed as percentage (%) of input. Bars and error bars represent means and SEM of at least three experimental repeats. Statistical analysis was performed using a one-tail two-sample Student's t-test compared to WT1 (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).