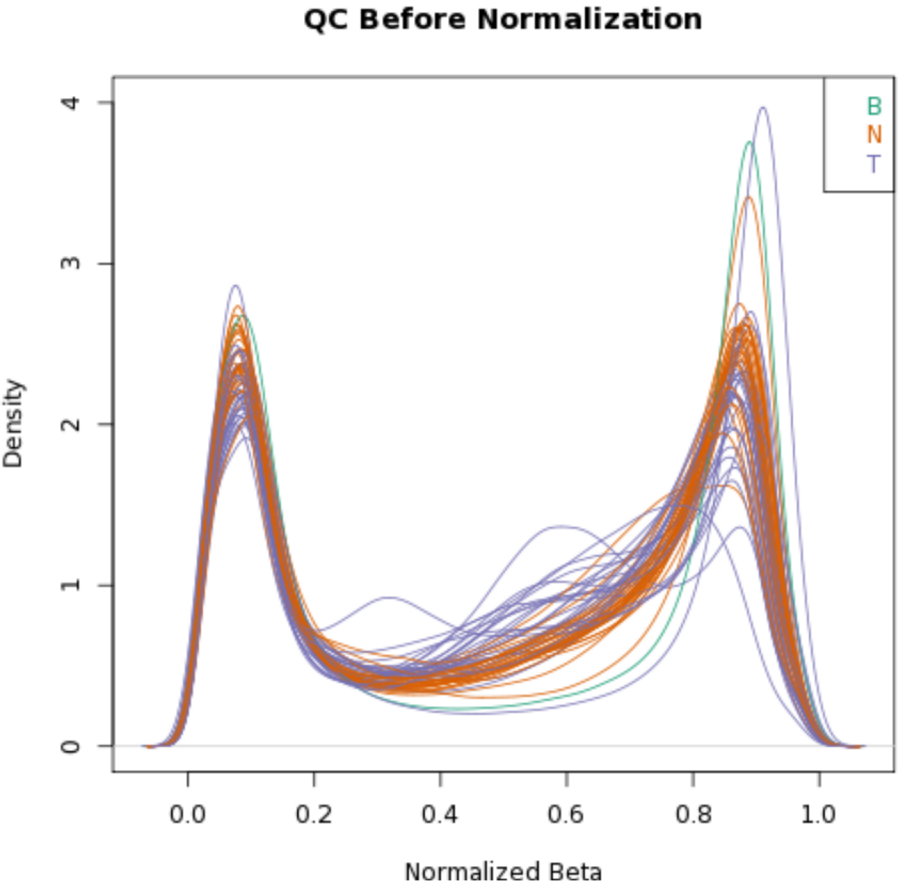
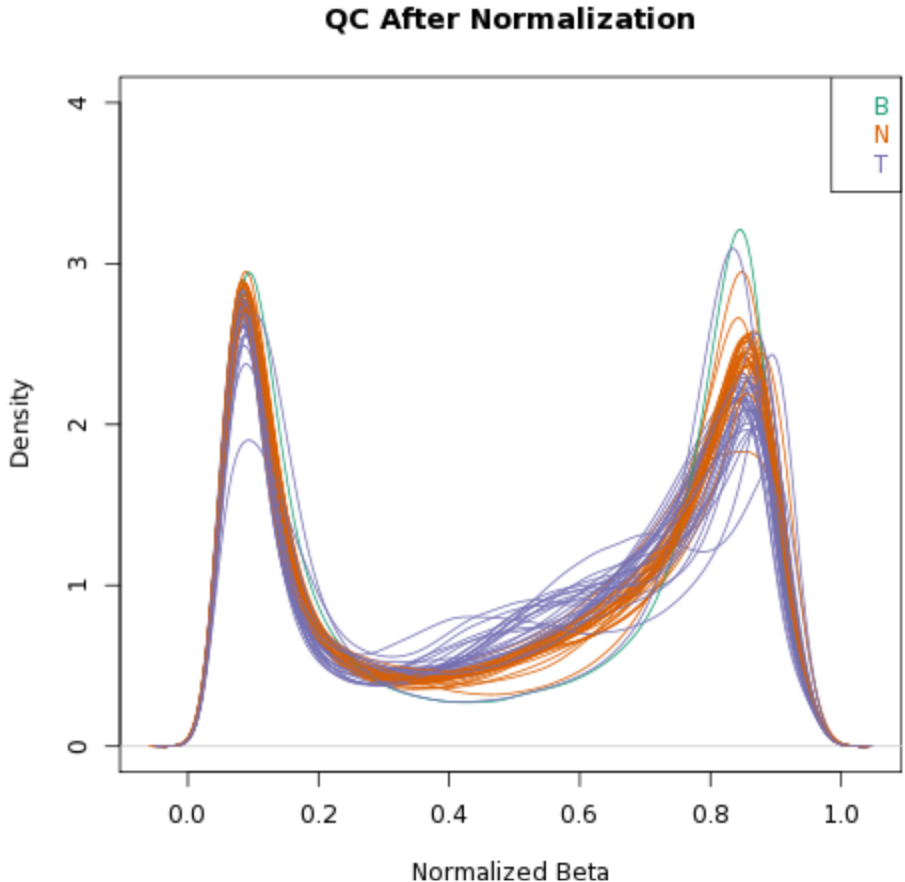
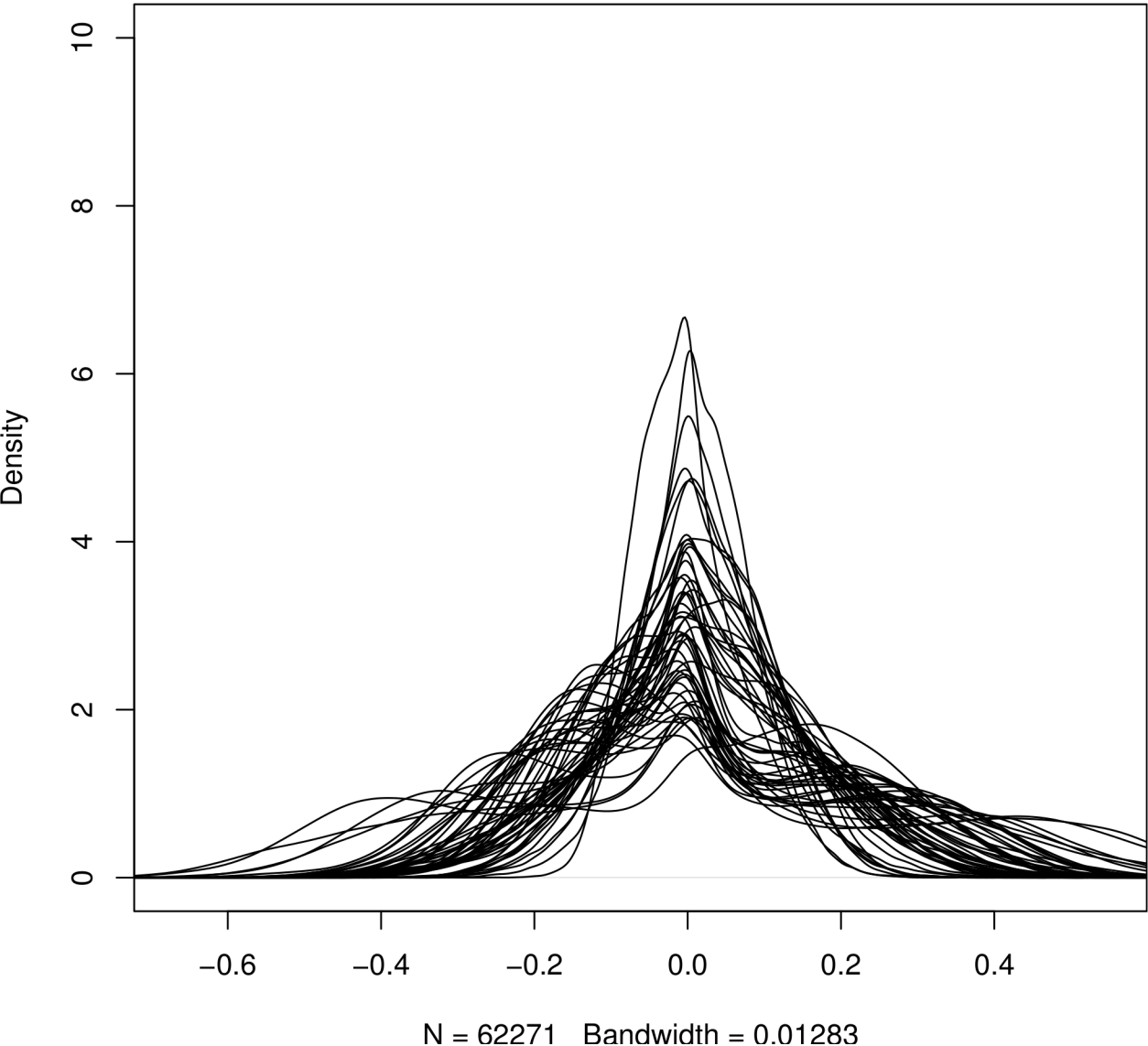
Supplementary Figure S1: Density plots of β (methylation intensities) before and after normalization.

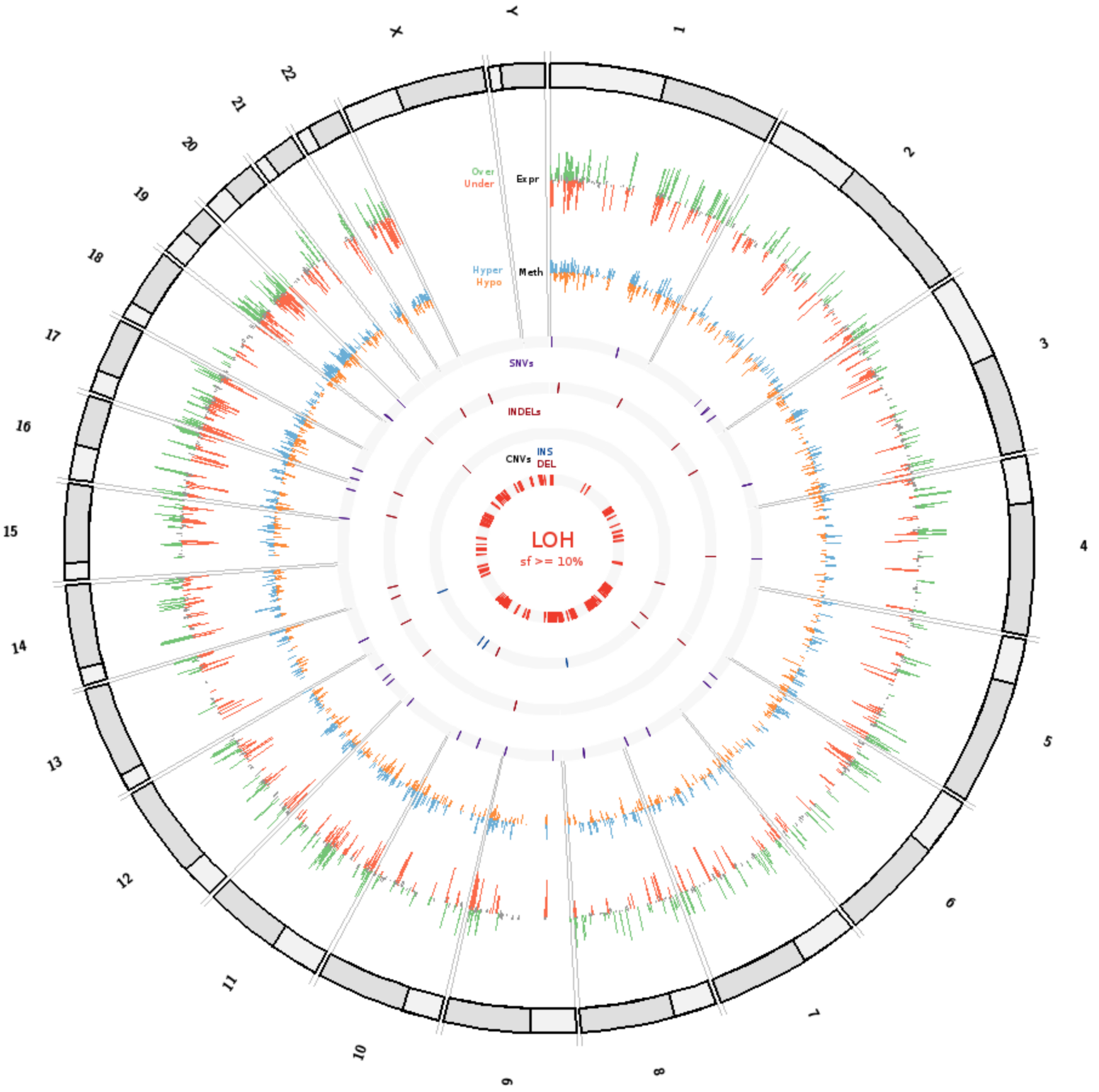




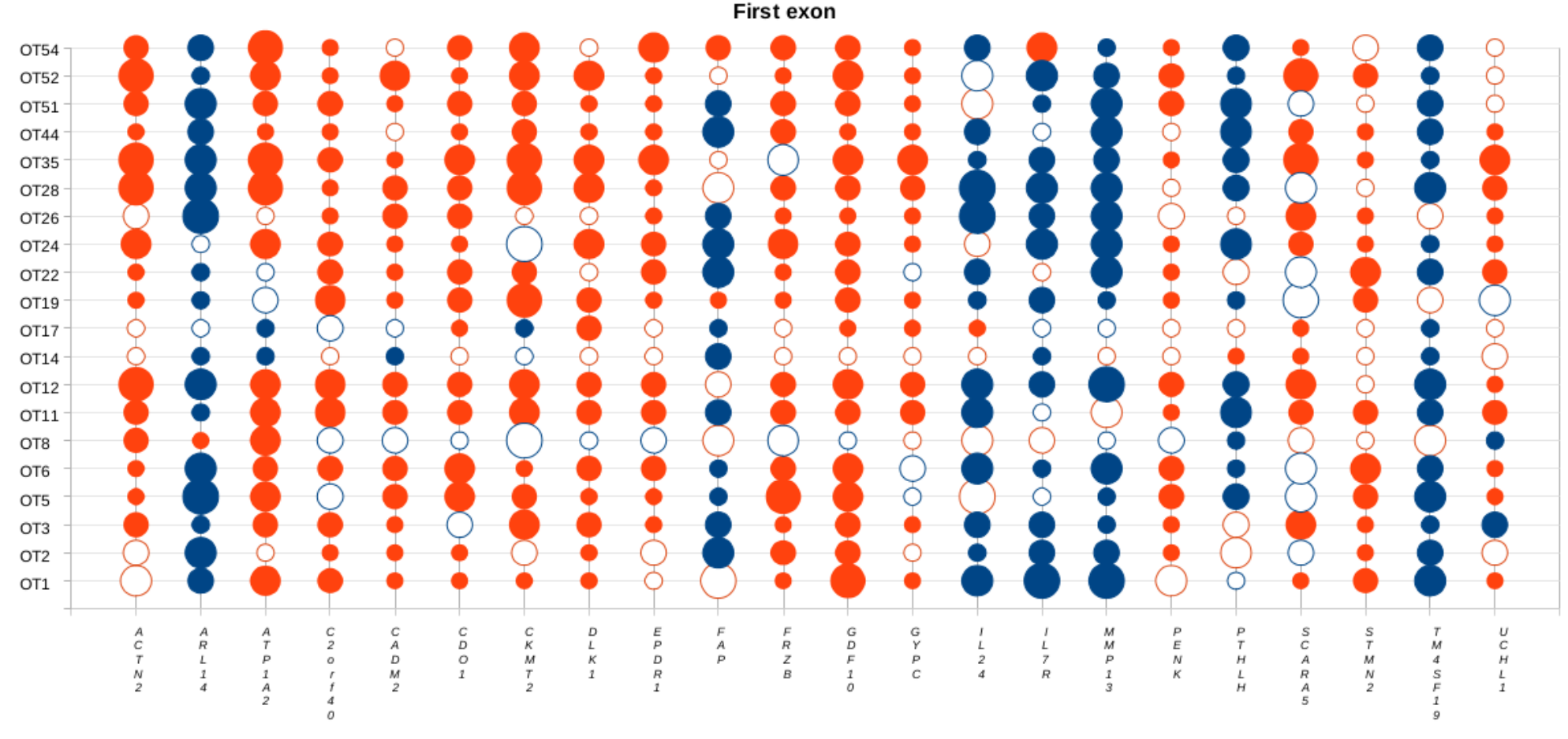
Supplementary Figure S2: Density plots of Δβ (difference in methylation intensities between tumor and its matched control) after normalization.

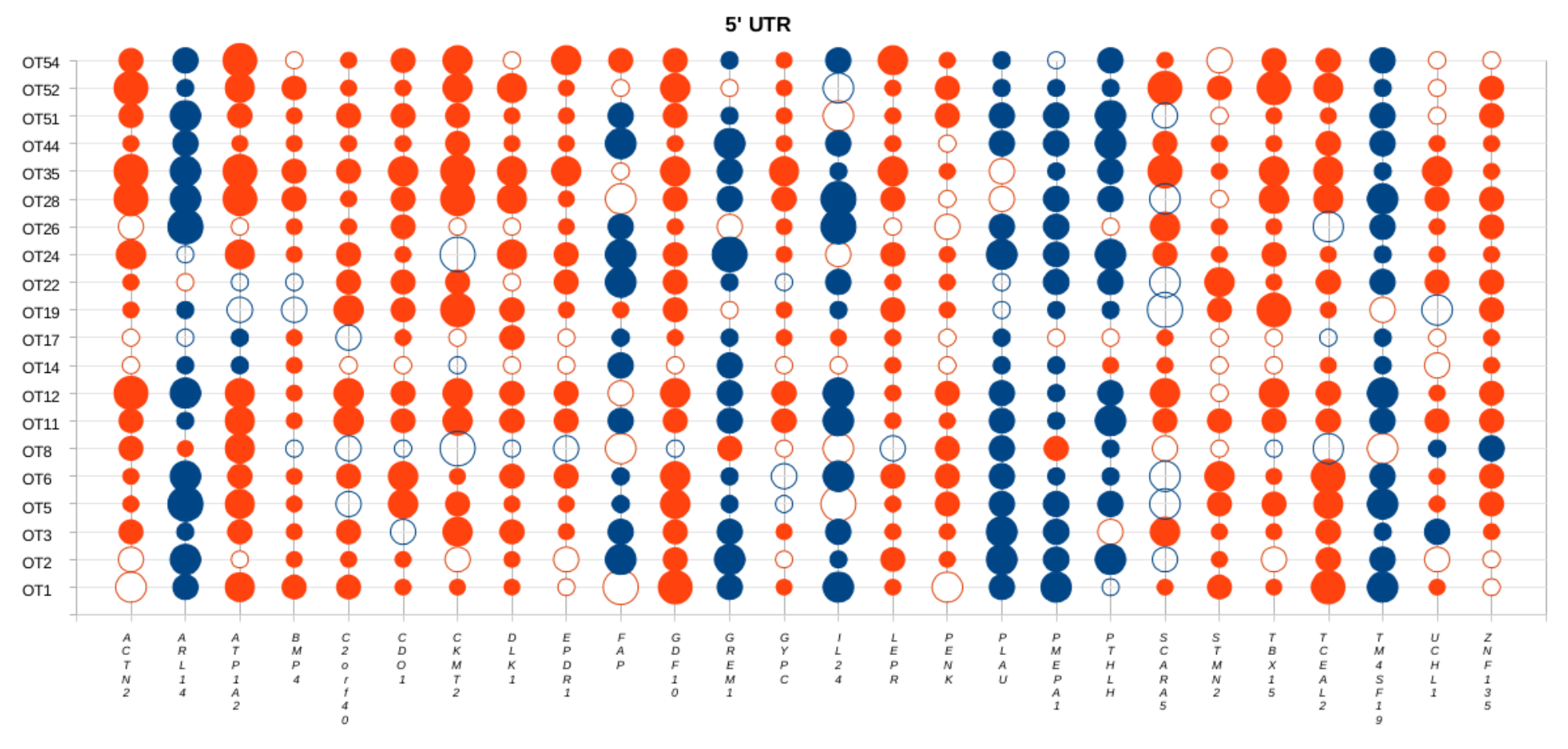


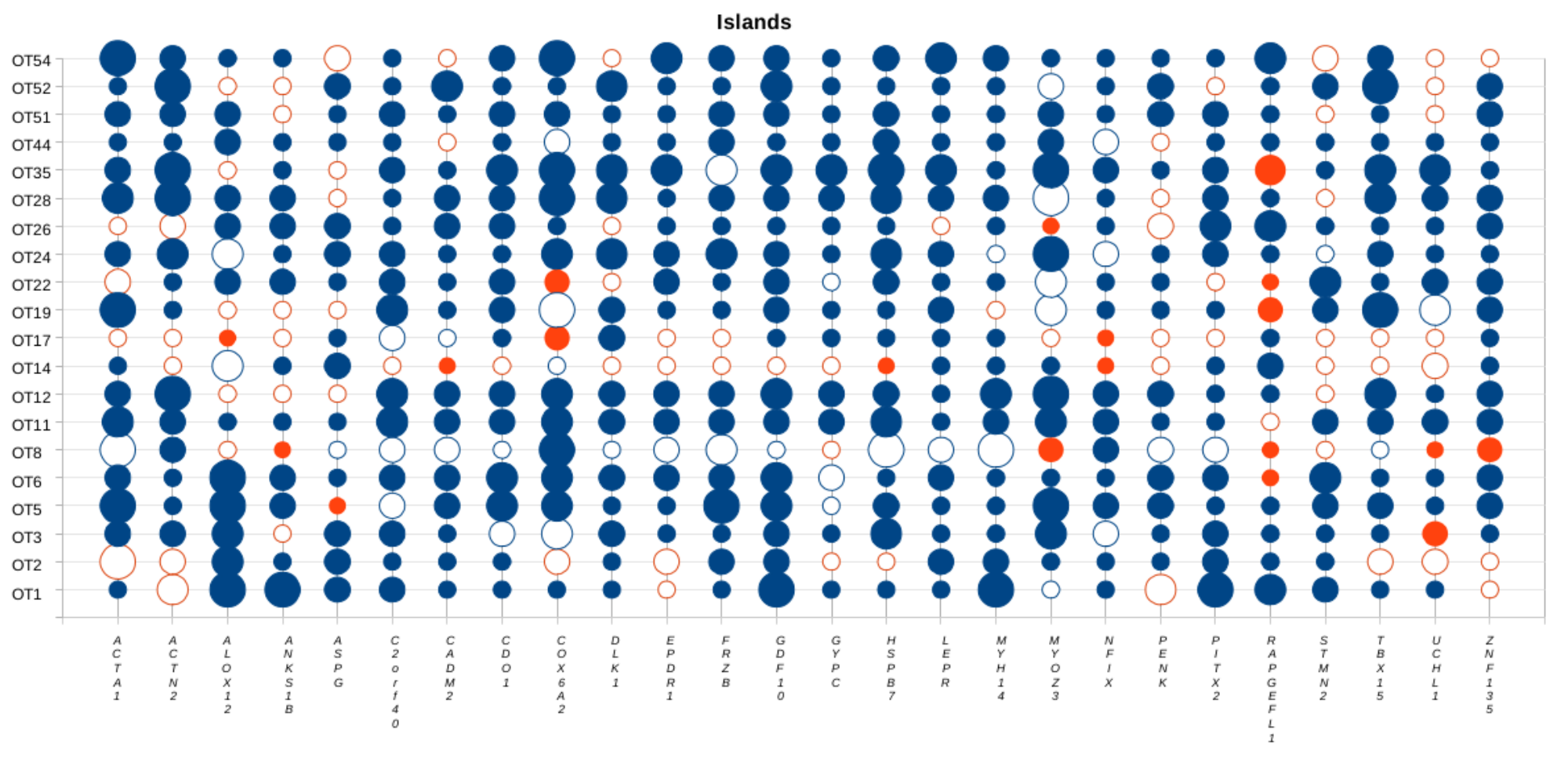
Supplementary Figure S3:Integrated circular representation of all variants (somatic mutations, Indels, Copy number variations, Loss of heterozygosity, Expression and Methylation) in 50 OTSCC samples using Circos.

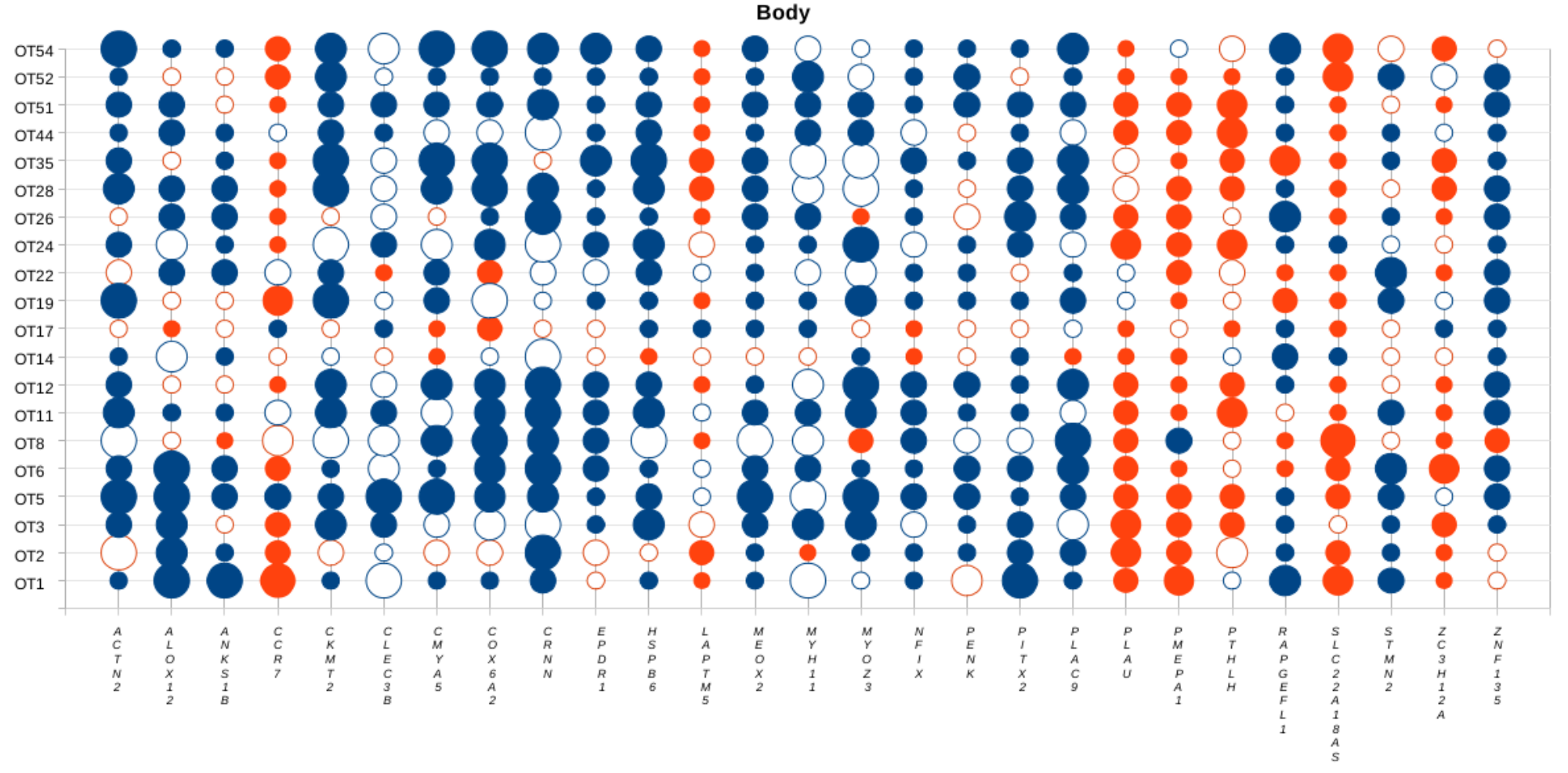


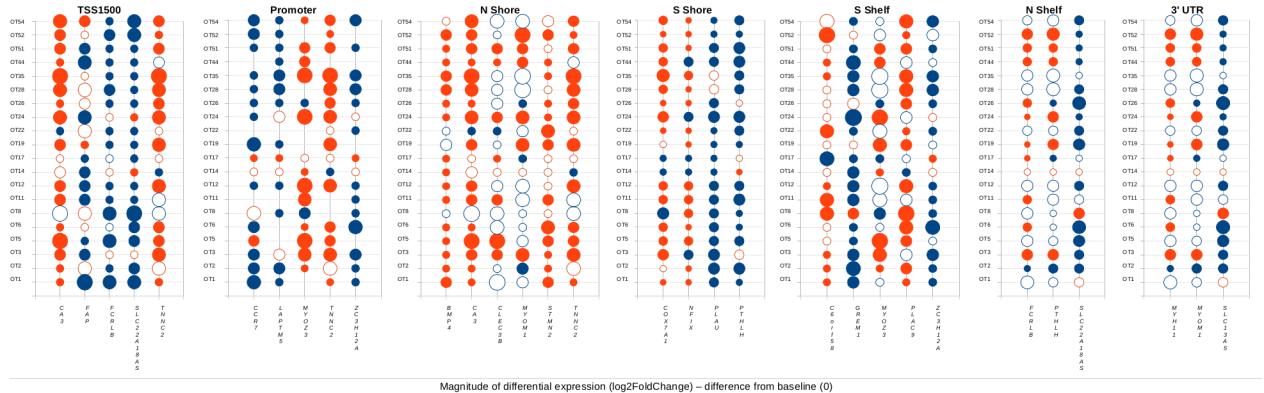
Supplementary Figure S4: Region-wise correlation between expression and methylation.
The correlation between differential expression of genes and differential methylation of various sub-regions of the genes (gene bodies, CpG islands, TSS1500, N Shore, S Shore, N Shelf, S Shelf, 5' UTR, 3' UTR, first exon and promoters) are represented as bubble tracks. Blue and orange colors indicate hypo- and hyper-methylation, respectively. Filled circles indicate a correlation in the expected direction, i.e. hyper-methylation and down-regulation, or hypo-methylation and up-regulation. Empty circles indicate a counter-intuitive correlation, namely, hyper-methylation and up-regulation, or hypo-methylation and down-regulation. The sizes of the circles are indicate of the magnitude of gene expression.



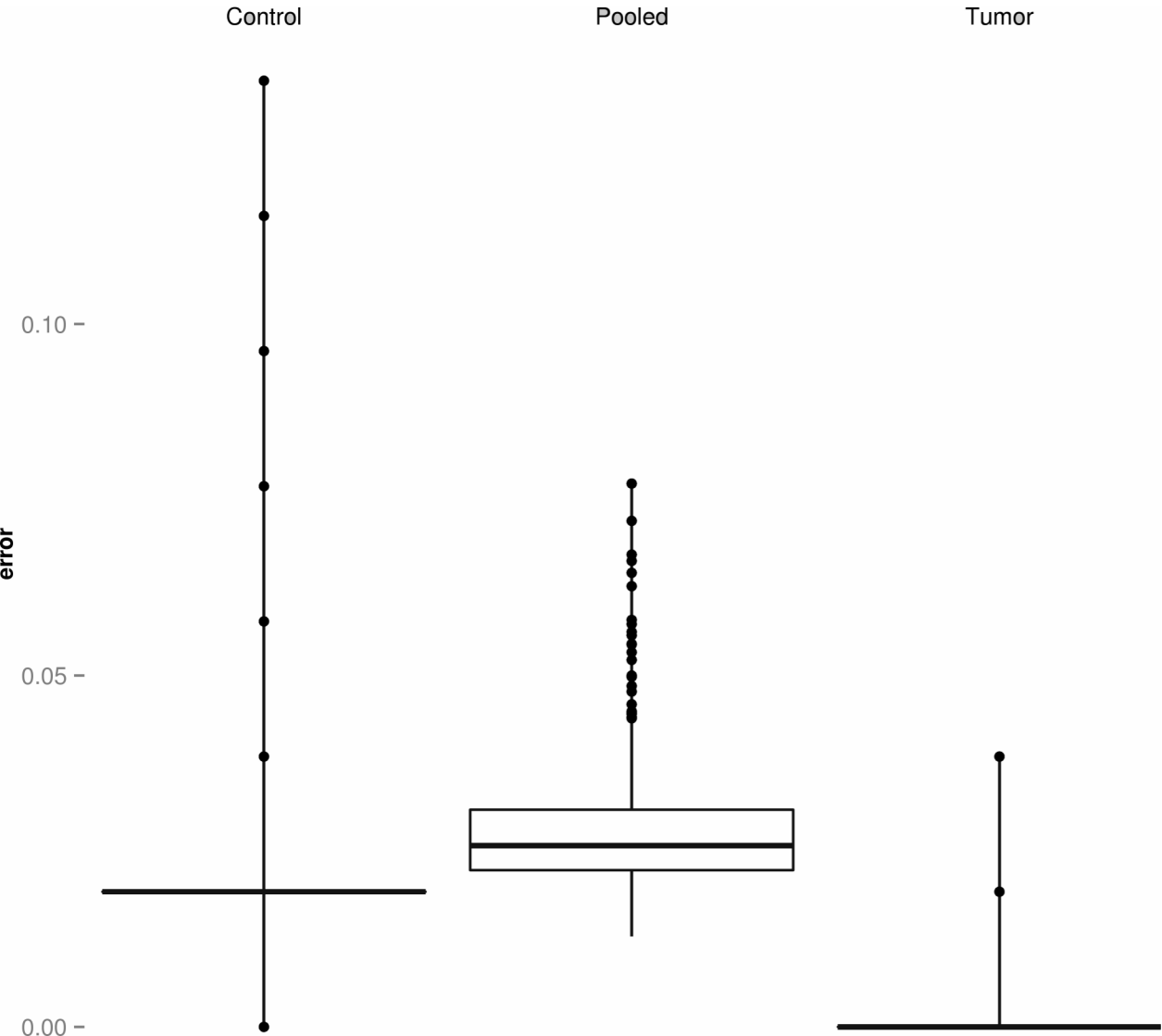

5' UTR
OT54
OT52
OT51
OT44
OT35
OT28
OT26
OT24
OT22
OT19
OT17
OT14
OT12
OT11
OT8
OT6
OT5
OT3
OT2
OT1
ACTN2
ARL14
ATP1A2
BMP4
C2orf40
CDO1
CKMT2
DLK1
EPDR1
FAP
GDF10
GREM1
GYPC
IL24
LEPR
PENK
PLAU
PMEPA1
PTHLH
SCARA5
STMN2
TBX15
TCEAL2
TM4SF19
UCHL1
ZNF135


Islands
OT54
OT52
OT51
OT44
OT35
OT28
OT26
OT24
OT22
OT19
OT17
OT14
OT12
OT11
OT8
OT6
OT5
OT3
OT2
OT1
ACTA1
ACTN2
ALOX12
ANKS1B
ASPG
C2orf40
CADM2
CDO1
COX6A2
DLK1
EPDR1
FRZB
GDF10
GYPC
HSPB7
LEPR
MYH14
MYOZ3
NFIX
PENK
PITX2
RAPGEFL1
STMN2
TBX15
UCHL1
ZNF135


Body
OT54
OT52
OT51
OT44
OT35
OT28
OT26
OT24
OT22
OT19
OT17
OT14
OT12
OT11
OT8
OT6
OT5
OT3
OT2
OT1
ACTN2
ALOX12
ANKS1B
CCR7
CKMT2
CLEC3B
CMYA5
COX6A2
CRNN
EPDR1
HSPB6
LAPTM5
MEOX2
MYH11
MYOZ3
NFIX
PENK
PITX2
PLAC9
PLAU
PMEPA1
PTHLH
RAPGEFL1
SLC22A18AS
STMN2
ZC3H12A
ZNF135

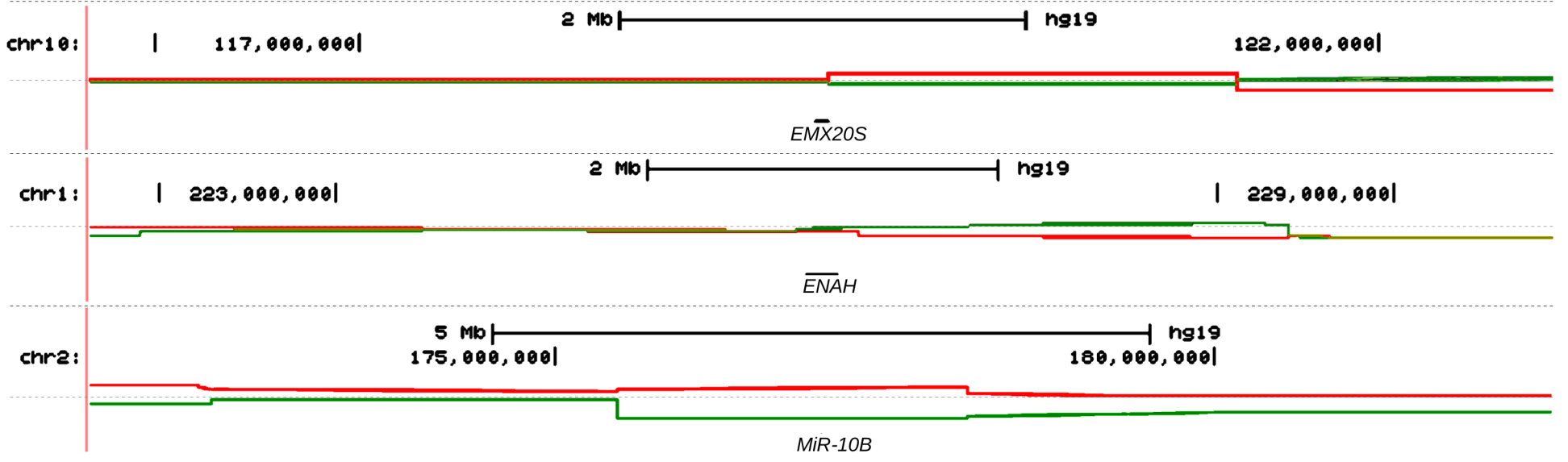

TSS1500
Promoter
N Shore
S Shore
S Shelf
N Shelf
3' UTR
OTS4
OTS2
OTS1
OTS44
OTS35
OTS28
OTS26
OTS24
OTS22
OTS19
OTS17
OTS14
OTS12
OTS11
OTS8
OTS6
OTS5
OTS3
OTS2
OTS1
CA3
FAP
FCRLB
SLC22A18AS
TNNC2
CCRT
LAPTM5
MYOZ3
BMP4
GEM1
COX7A1
NFIX
PLAU
PTHLH
CELF3
PLAC9
ZC3H12A
FCRLB
PTTLH
SLC22A18AS
MYH11
MYOM1
SLC13A5
Magnitude of differential expression (log2FoldChange) – difference from baseline (0)
>0.69
0.69
0.46
0.2
Hypo-methylated & Over-expressed
Hyper-methylated & Under-expressed
0.23
Hypo-methylated & Under-expressed
Hypo-methylated & Over-expressed

Supplementary Figure S5: 0.632+ error in random forest predictions using the first (most stringent) training set, for the tumor, matched control, and tumor/matched control tissues



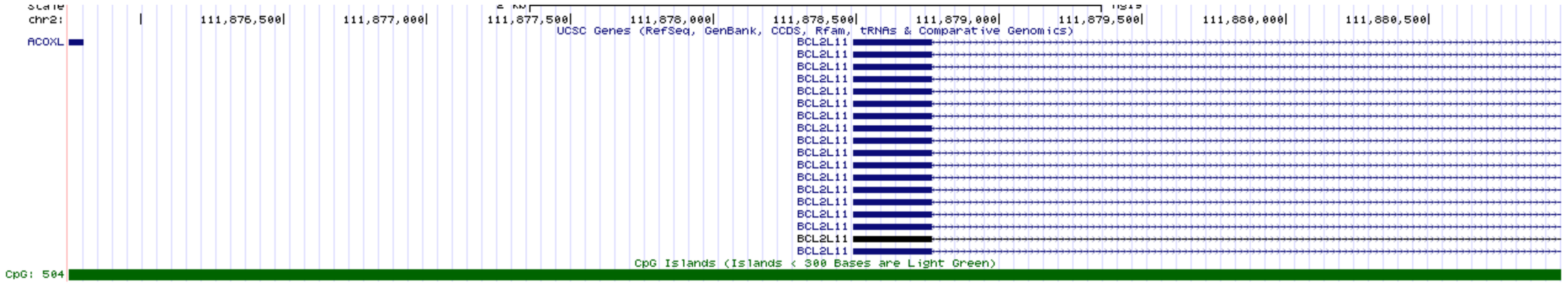
Supplementary Figure S6: Methylation status of genes harboring these DMRs in publicly available cell line data. Relevant UCSC Genome Browser tracks were visualized for the four genes (GPER1, OR2T6, TTLL8 and RHPN1).

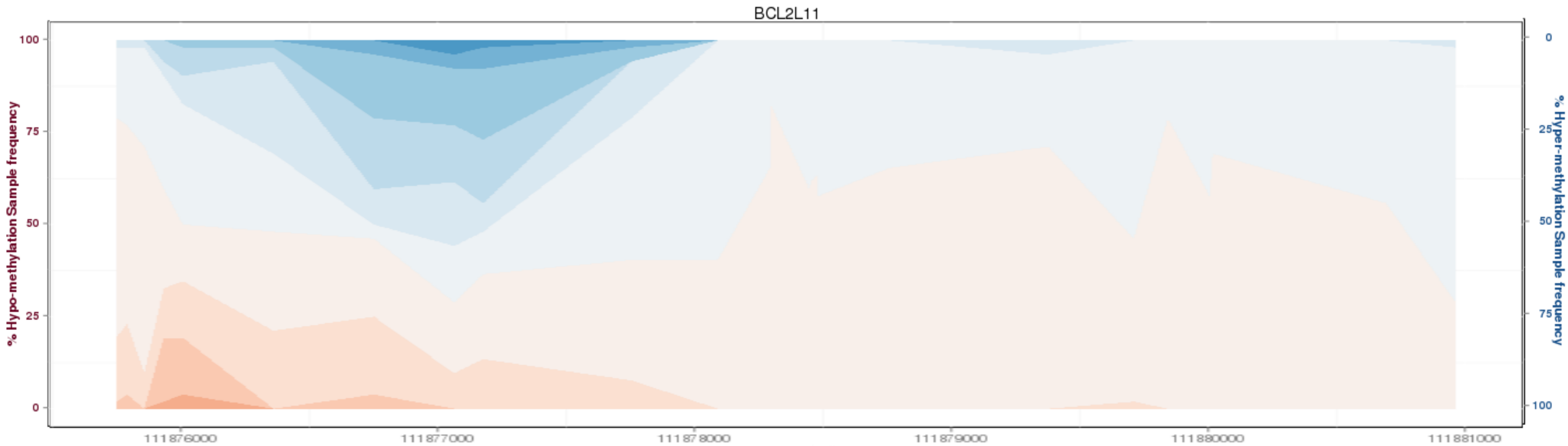
Supplementary Figure S7: Median differential methylation and expression profiles of regions flanking ENAH, EMX2OS and MiR10B genes. The green line represents differential expression and the red line represents differential methylation. The grey dashed line depicts a baseline of median log2FC = 0 and median Δβ = 0



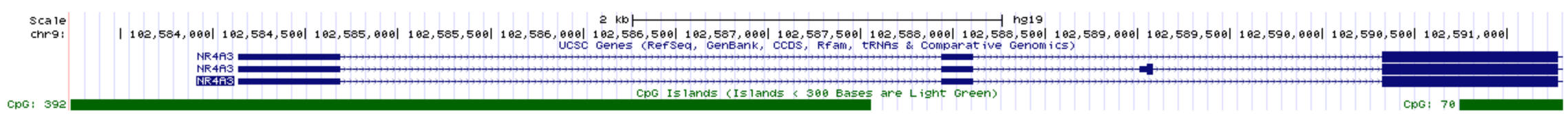
Supplementary Figure S8: Differential methylation in CpG islands of *BCL2L11* (A) and *NR4A3* (B) genes represented as stacked area charts of % samples conforming to various delta beta ranges (indicated as a red to blue color gradient, where the darkest shades of red and blue indicate the highest levels of hypo- and hyper-methylation, respectively). Gene structure (with exons as solid boxes and introns as lines with arrows indicating direction of transcription) and CpG density tracks from the UCSC GenomeBrowser, for the same genomic coordinates, are juxtaposed for reference.

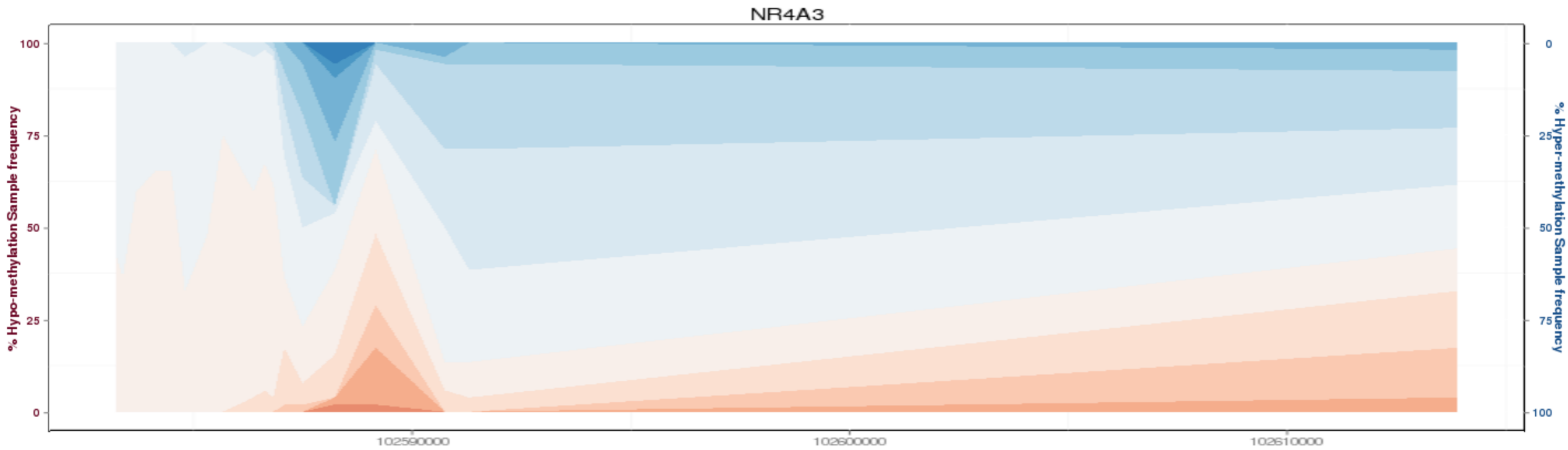
A



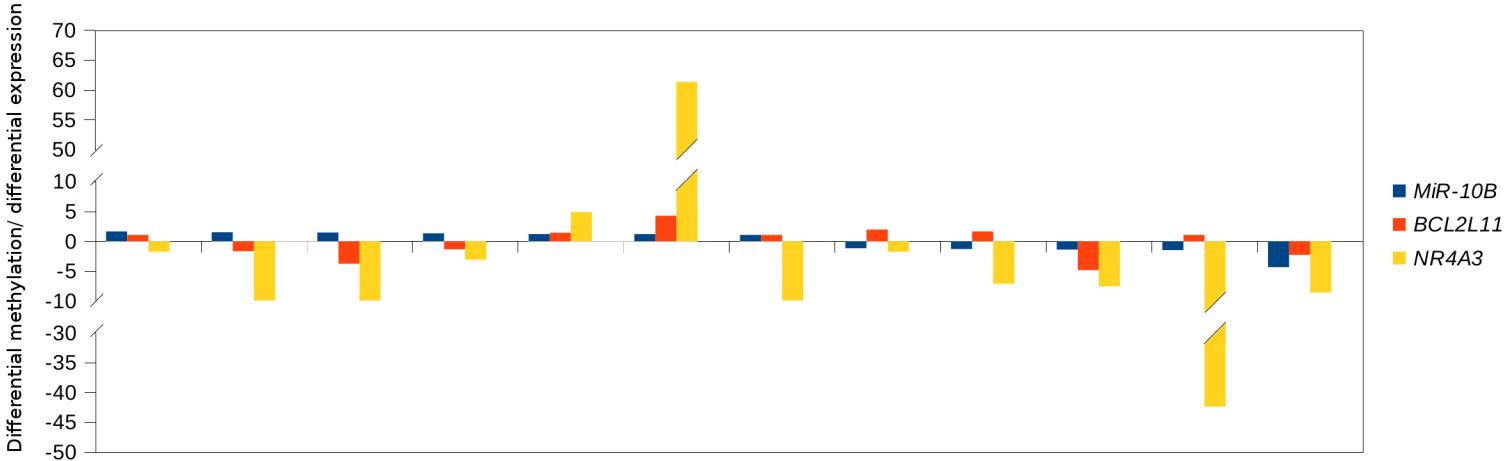


B



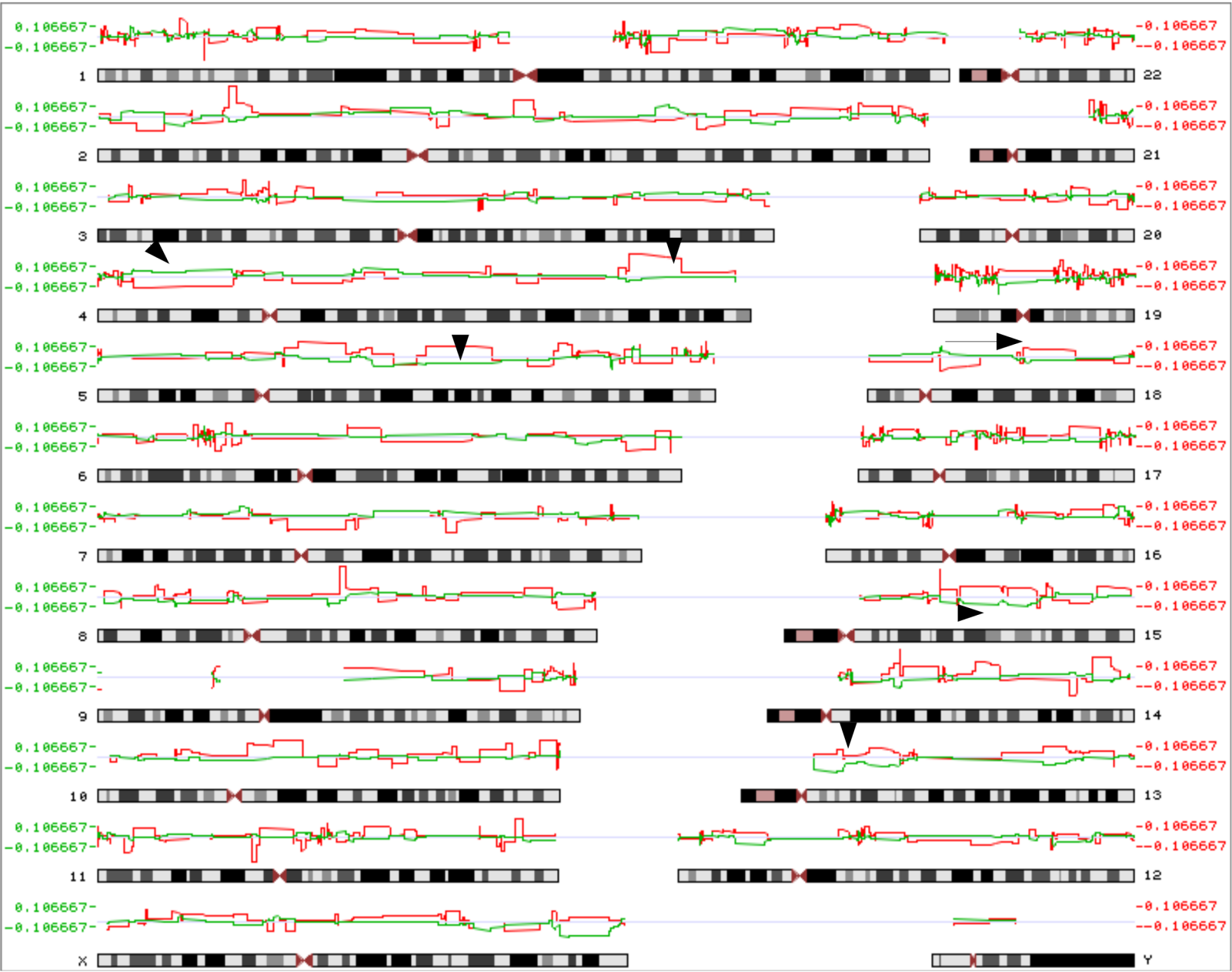


Supplementary Figure S9 Experimental validation of differential methylation in *MiR-10B*, and differential expression in its downstream target genes, *NR4A3* and *BCL2L11*, in 12 additional tumor:matched control pairs.



Supplementary Figure S10: NR4A3 differential expression status in the discovery set (N=21), validation set (N=12) and TCGA Oral Tongue cohort (N=12)

Supplementary Figure S11: Genome-wide correlation between differential methylation and differential expression (log2FoldChange) in island DMRs. The red lines represent differential methylation and the green lines represent differential expression. The arrows highlight regions of functional importance.



Supplementary Figure S12: Delta beta trend spanning DMPs/DMRs discovered as part of the minimal signature. Red dot represents the median delta beta across samples for the discovered DMP(s), while the blue dots are the median values for the neighboring probes. The blue line is an exponentially smoothed (alpha = 0.1) median delta beta trend.