

Storage batch

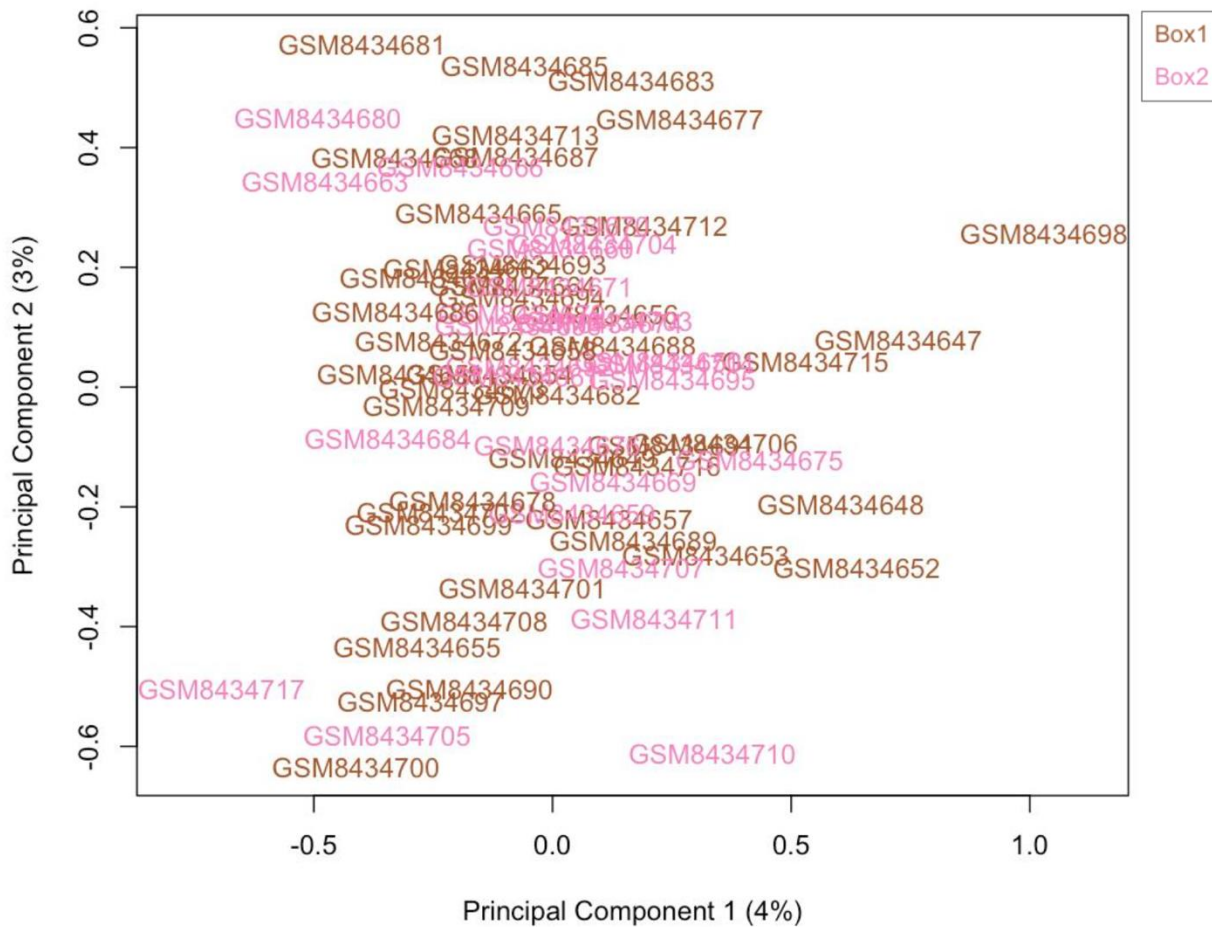


Figure S1. Results of multi dimensional scaling analysis. In the analysis normalized, filtered and transformed to M-values data was used. Two principal components were visualized including 1000 top genes whose variances contributed the most to the selected components. Label colors indicate DNA storage batches.

Extraction batch

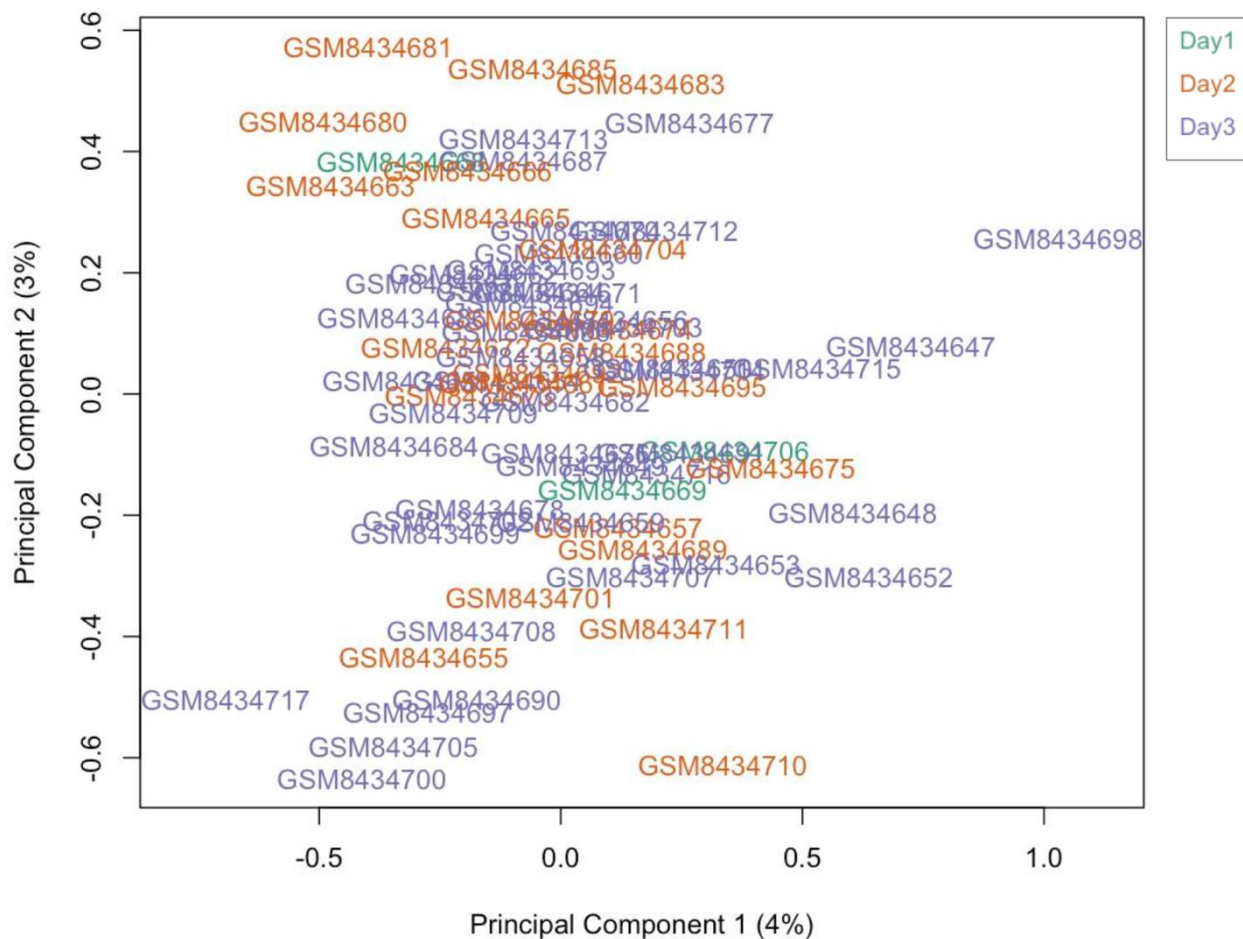


Figure S2. Results of multi dimensional scaling analysis. In the analysis normalized, filtered and transformed to M-values data was used. Two principal components were visualized including 1000 top genes whose variances contributed the most to the selected components. Label colors indicate DNA extraction batches.

Array batch

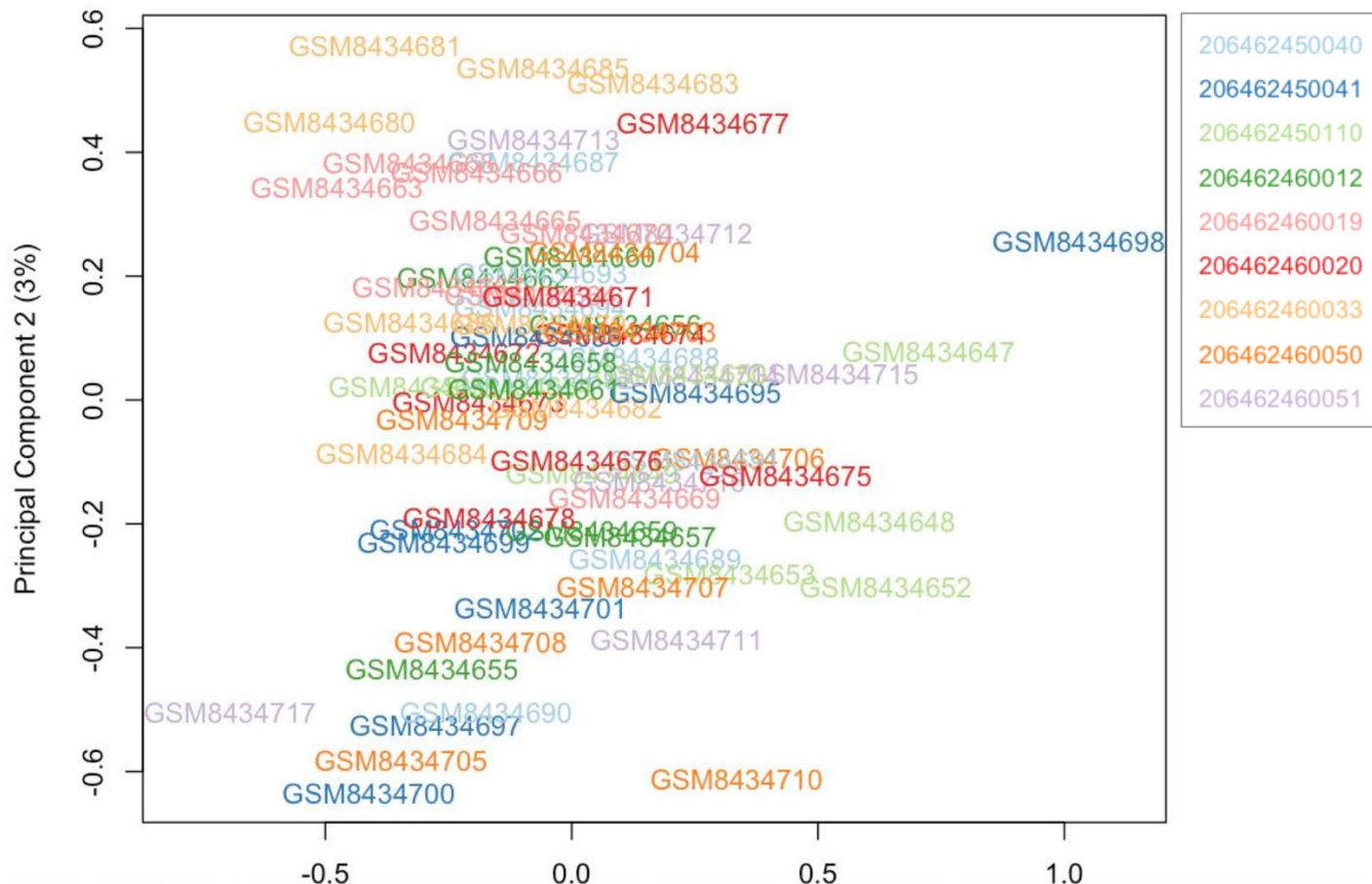


Figure S3. Results of multi dimensional scaling analysis. In the analysis normalized, filtered and transformed to M-values data was used. Two principal components were visualized including 1000 top genes whose variances contributed the most to the selected components. Label colors indicate methylation array batches.

Sex

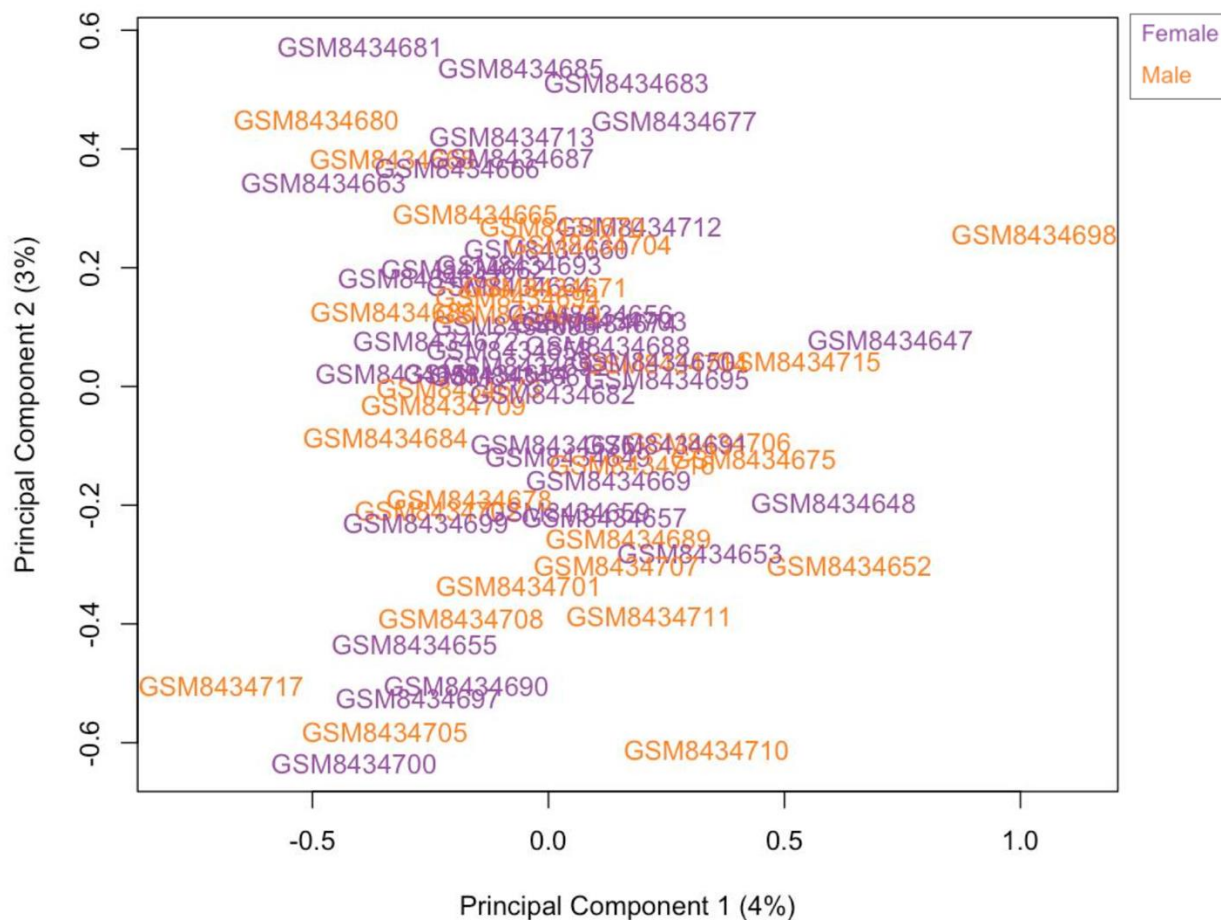


Figure S4. Results of multi dimensional scaling analysis. In the analysis normalized, filtered and transformed to M-values data was used. Two principal components were visualized including 1000 top genes whose variances contributed the most to the selected components. Label colors correspond to sample sex.

Joined cohort

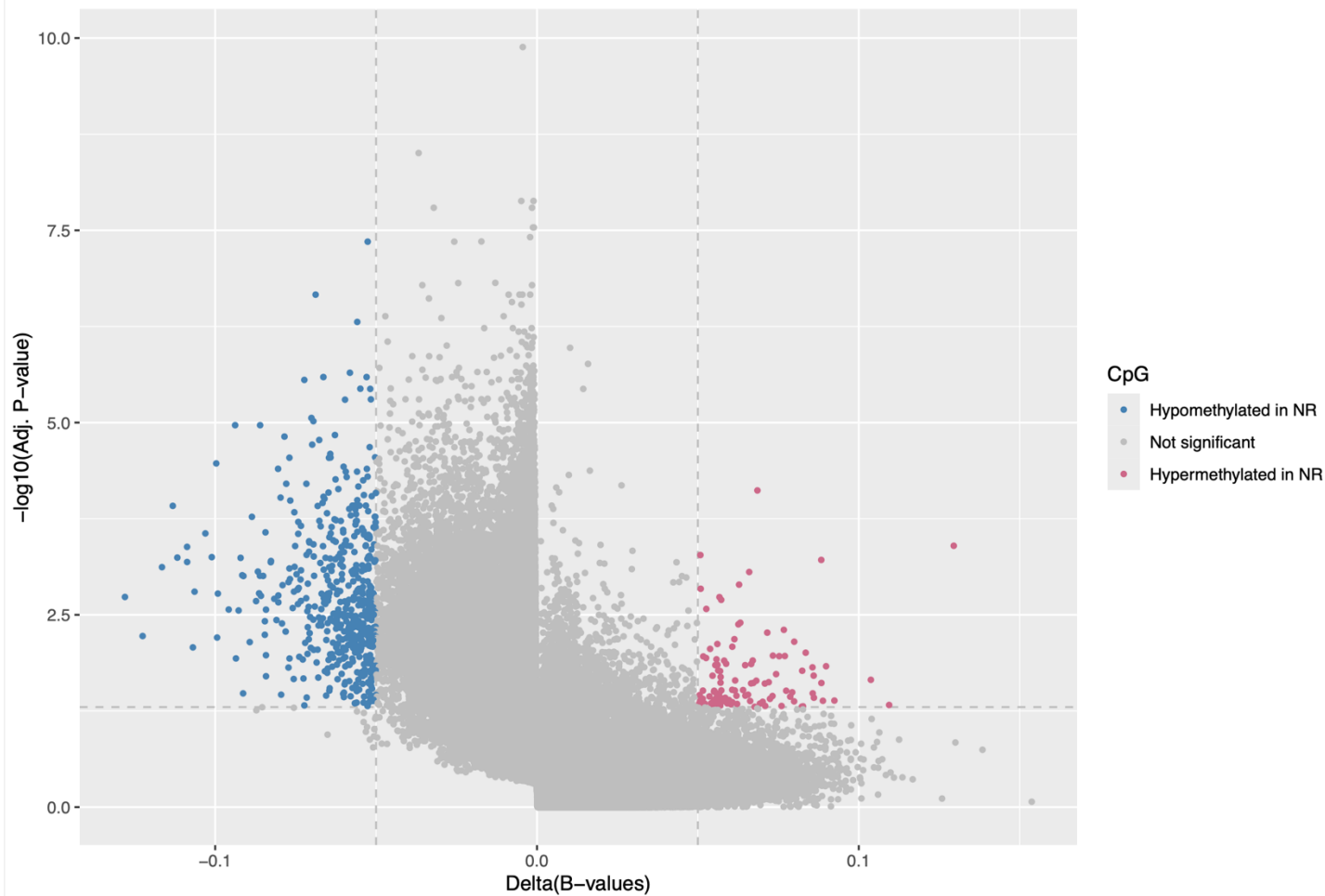


Figure S6. Volcano plot representing BH-adjusted p-values and methylation difference Delta(B-values) in all CpG sites compared between NR and R groups in aggregated cohort of females and males. Colored dots represent differentially methylated CpG sites (with methylation difference > 5% and BH-adjusted p-value < 0.05).

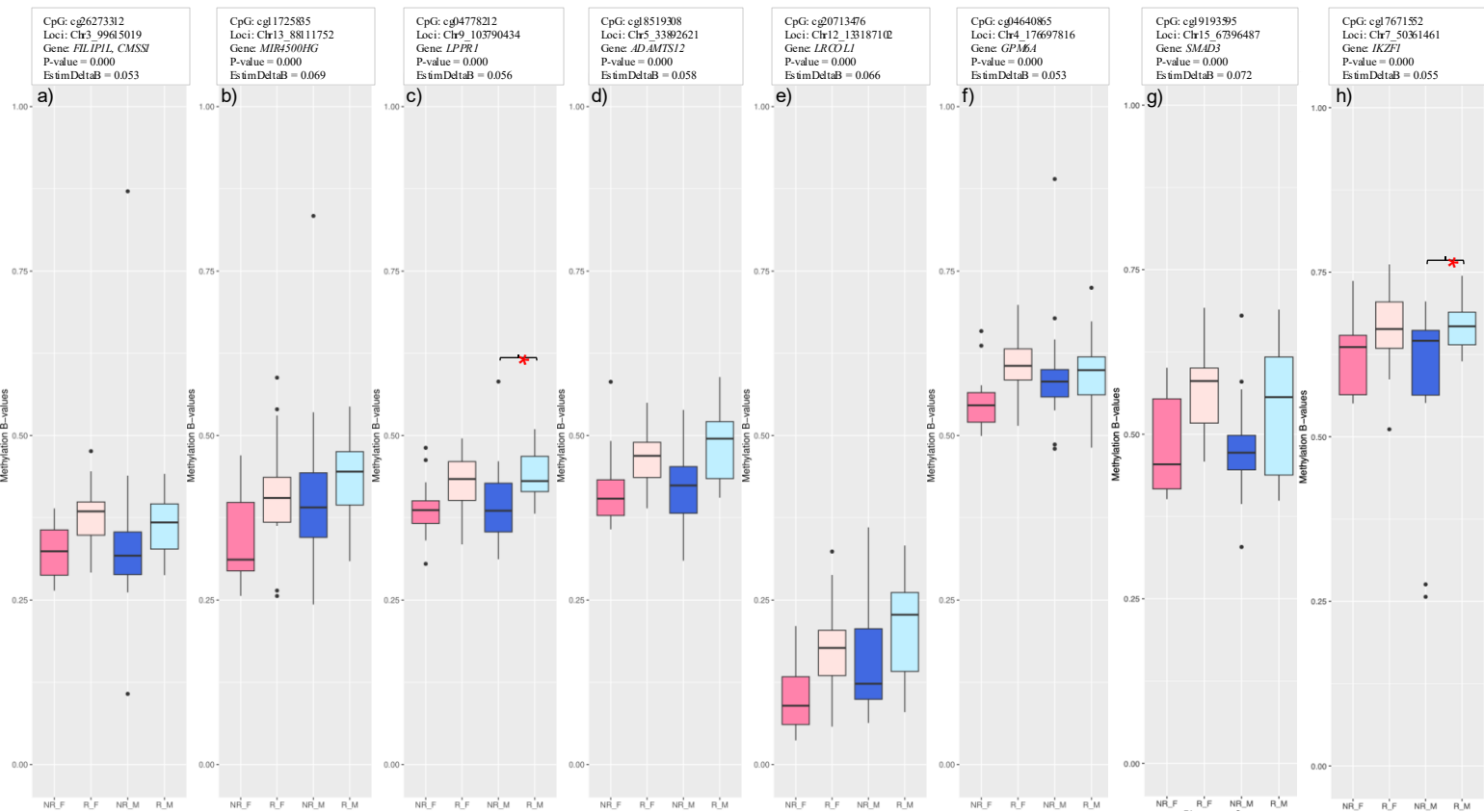


Figure S7. Methylation box plots of top genic CpG sites from sex-joined analysis. Figure visualizes a) cg26273312, b) cg11725835, c) cg04778212, d) cg18519308, e) cg20713476, f) cg04640865, g) cg19193595, h) cg17671552. Plots are ordered from left to right by increasing adjusted p-value. Asterisks indicate significant differences between R and NR groups.

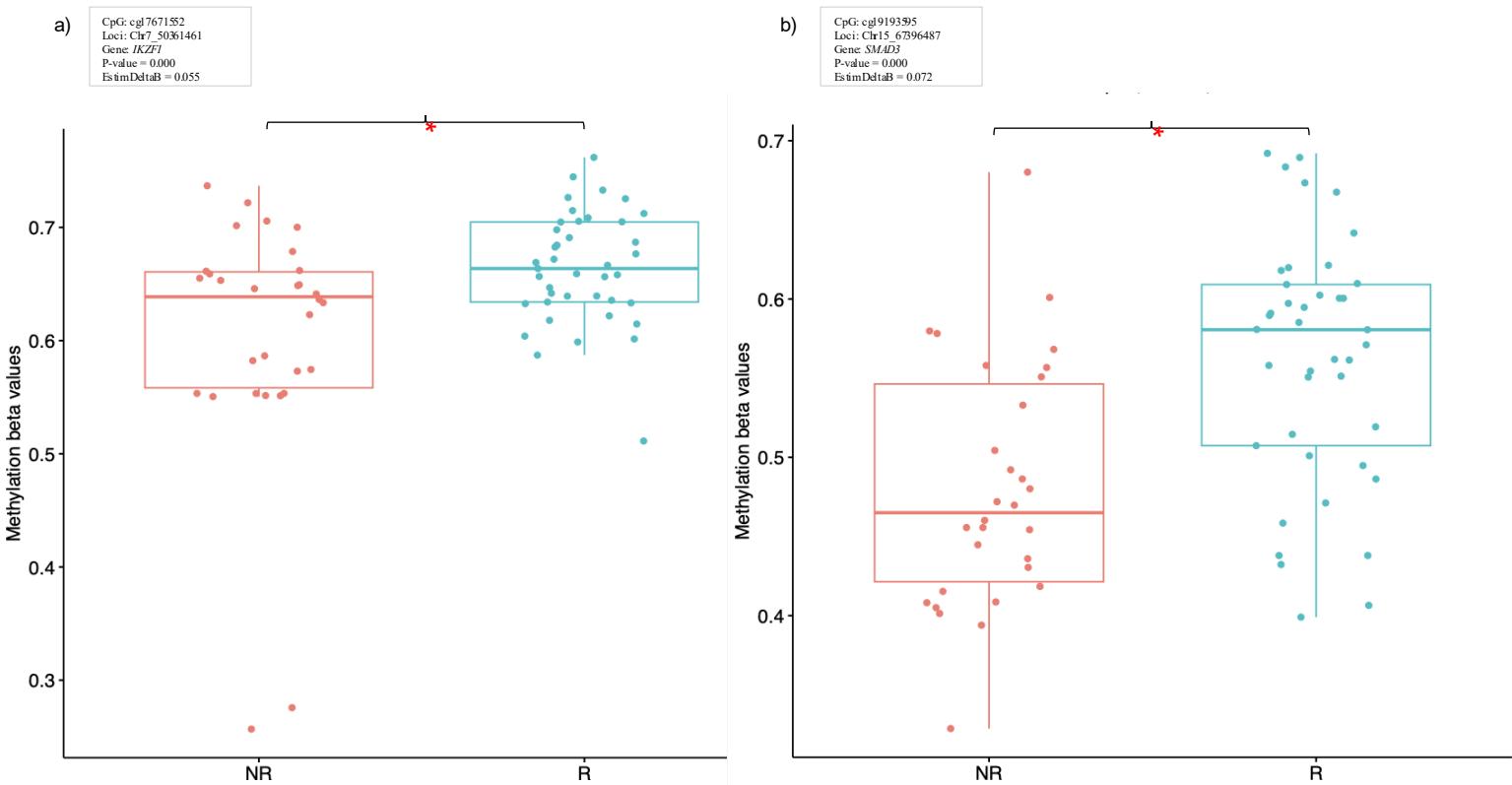


Figure S8. Methylation box plot. Figure visualizes a) cg17671552 CpG site within *IKZF1* gene and b) cg19193595 CpG site within *SMAD3* gene in studied cohort. Asterisks indicate significant differences between R and NR groups.

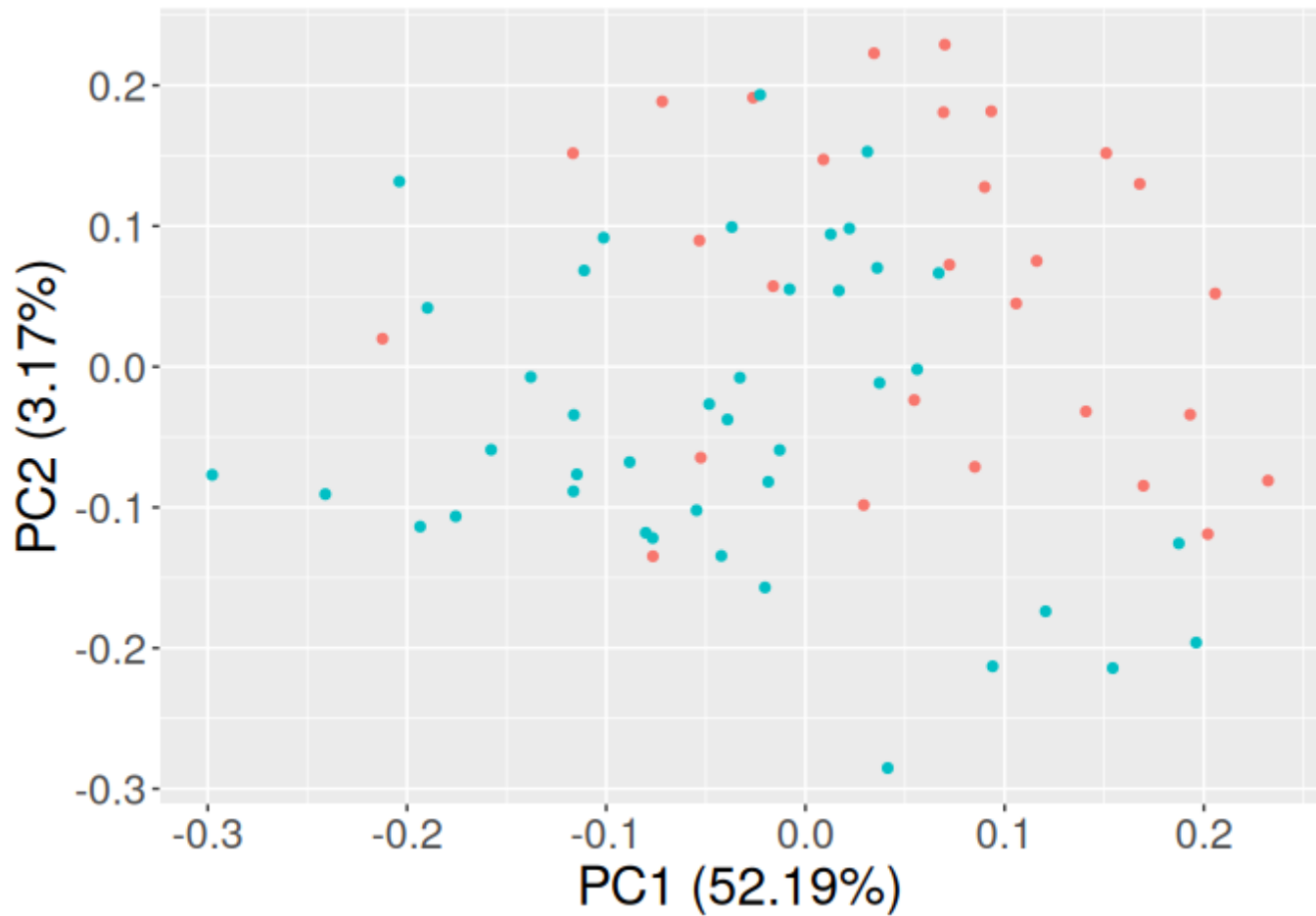


Figure S9. Summary of principal component analysis results. In the analysis we used normalized β -values of 631 DMPs emerged as significantly differentially methylated between R (turquoise dots) and NR (red dots) in sex-joined cohort.

Female cohort

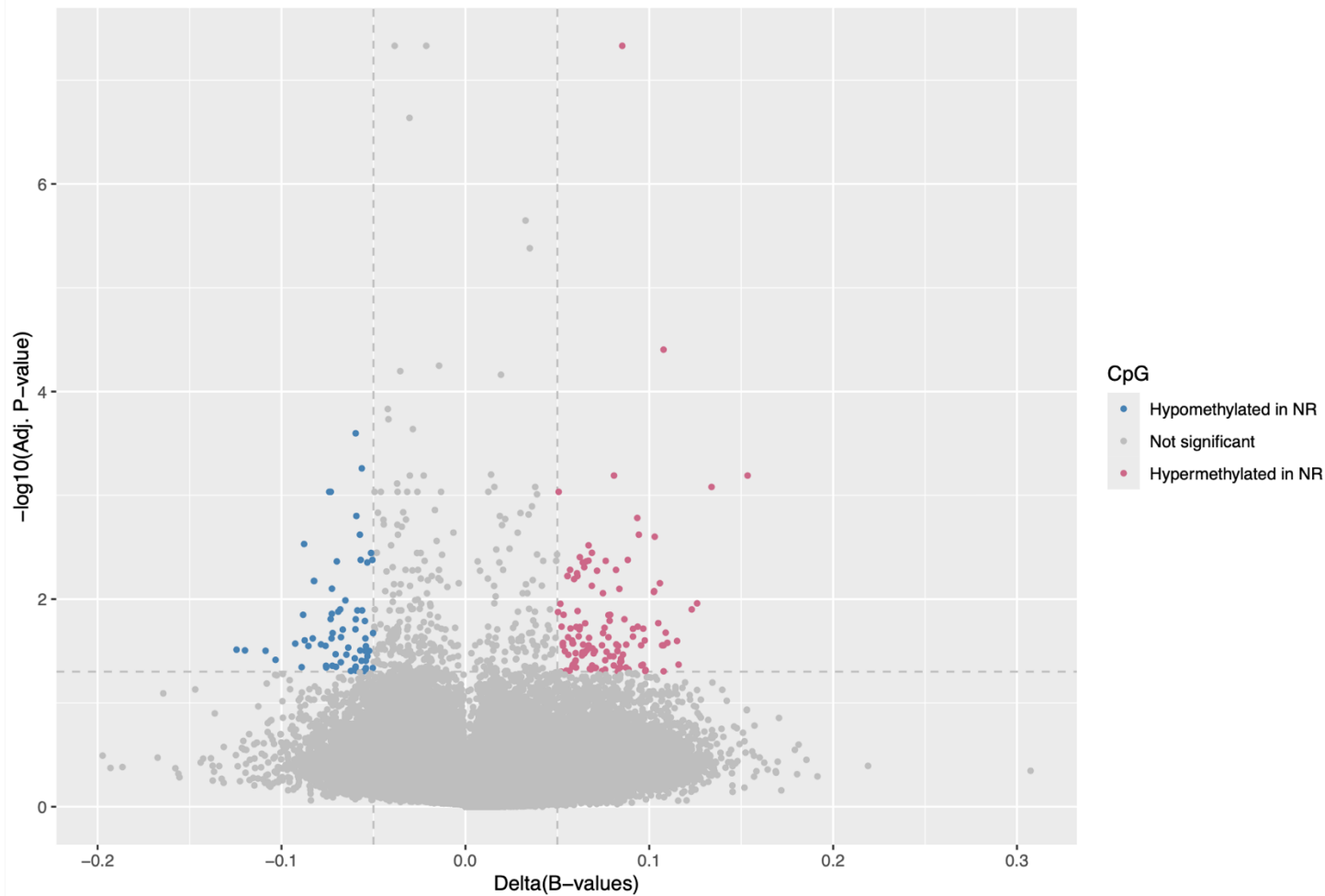


Figure S10. Volcano plot representing BH-adjusted p-values and methylation difference $\Delta(B\text{-values})$ in all CpG sites compared between NR and R groups in female cohort. Colored dots represent differentially methylated CpG sites (with methylation difference $> 5\%$ and BH-adjusted p-value < 0.05).

In Females

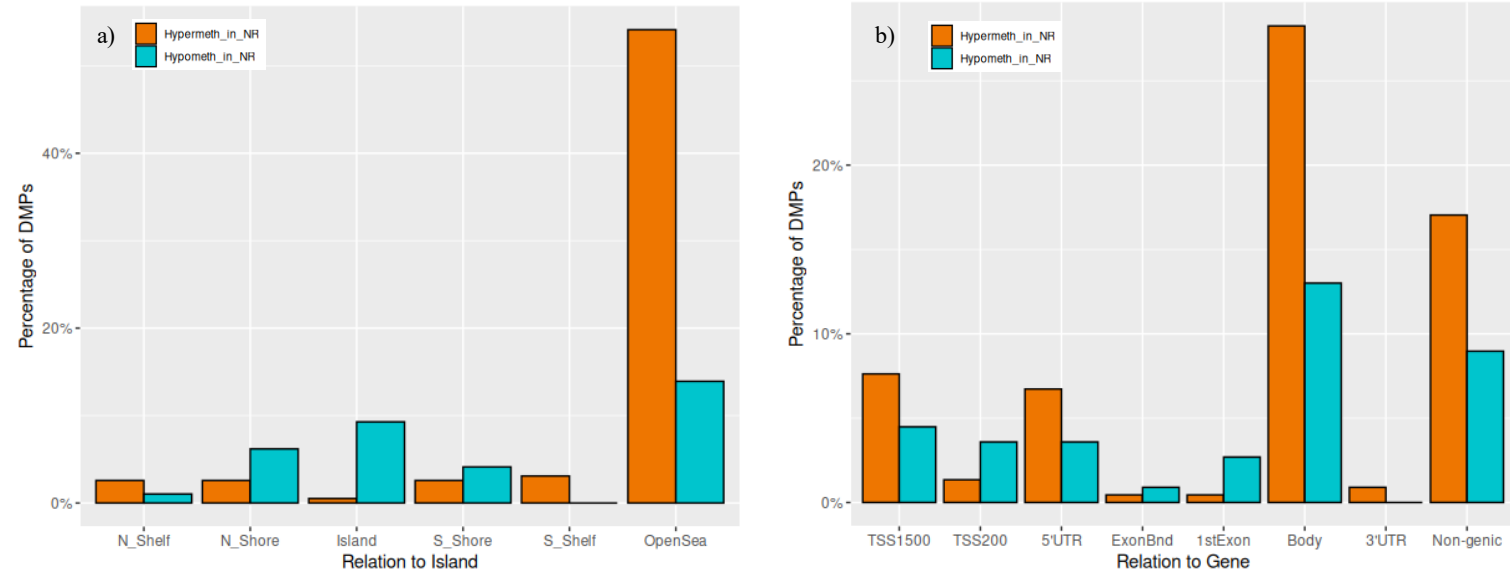


Figure S11. Distribution of DMPs emerged from DMA of female cohort (hyper and hypo-methylated). Barplots visualize distribution in relation to a) CpG islands and b) gene regions. Y-axis indicates percentage of significant CpGs belonging to a particular subregions.

Similar to the trends observed in the analysis of the entire cohort (Figure 1), the differential methylation signal tended to accumulate in the open sea of CpG islands (68% of all DMPs) and in the body of genes (56% of genic DMPs). However, unlike sex-independent DMPs, the gene body and open sea regions were mostly hypermethylated in the NR group.

Male cohort

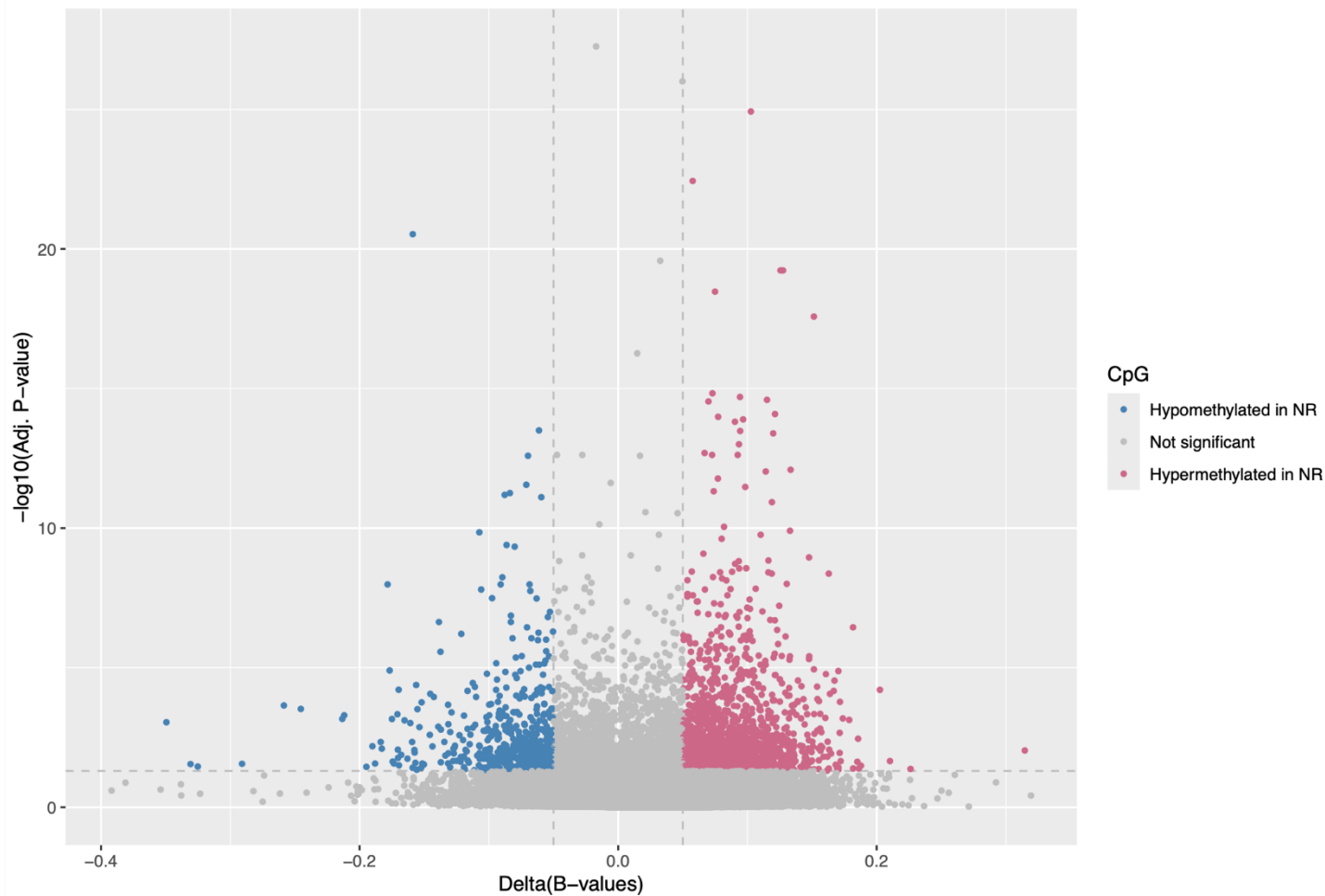


Figure S12. Volcano plot representing BH-adjusted p-values and methylation difference Delta(B-values) in all CpG sites compared between NR and R groups in female cohort. Colored dots represent differentially methylated CpG sites (with methylation difference $> 5\%$ and BH-adjusted p-value < 0.05).

In Males

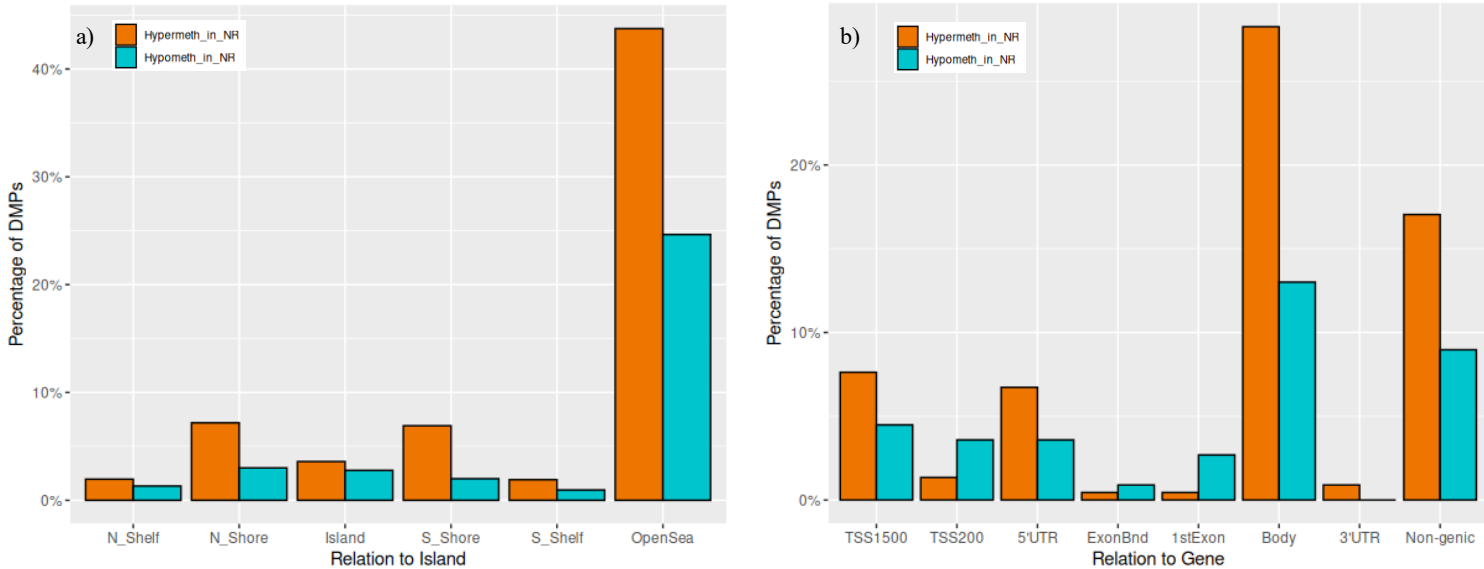


Figure S13. Distribution of DMPs emerged from DMA of male cohort (hyper and hypo-methylated). Barplots visualize distribution in relation to a) CpG islands and b) gene regions. Y-axis indicates percentage of significant CpGs belonging to a particular subregions.

Most (68%) of the total DMPs were spread along the open sea of CpG islands and 57% of genic DMPs were located in the gene body. Both overrepresented subregions were predominantly hypermethylated in NR.

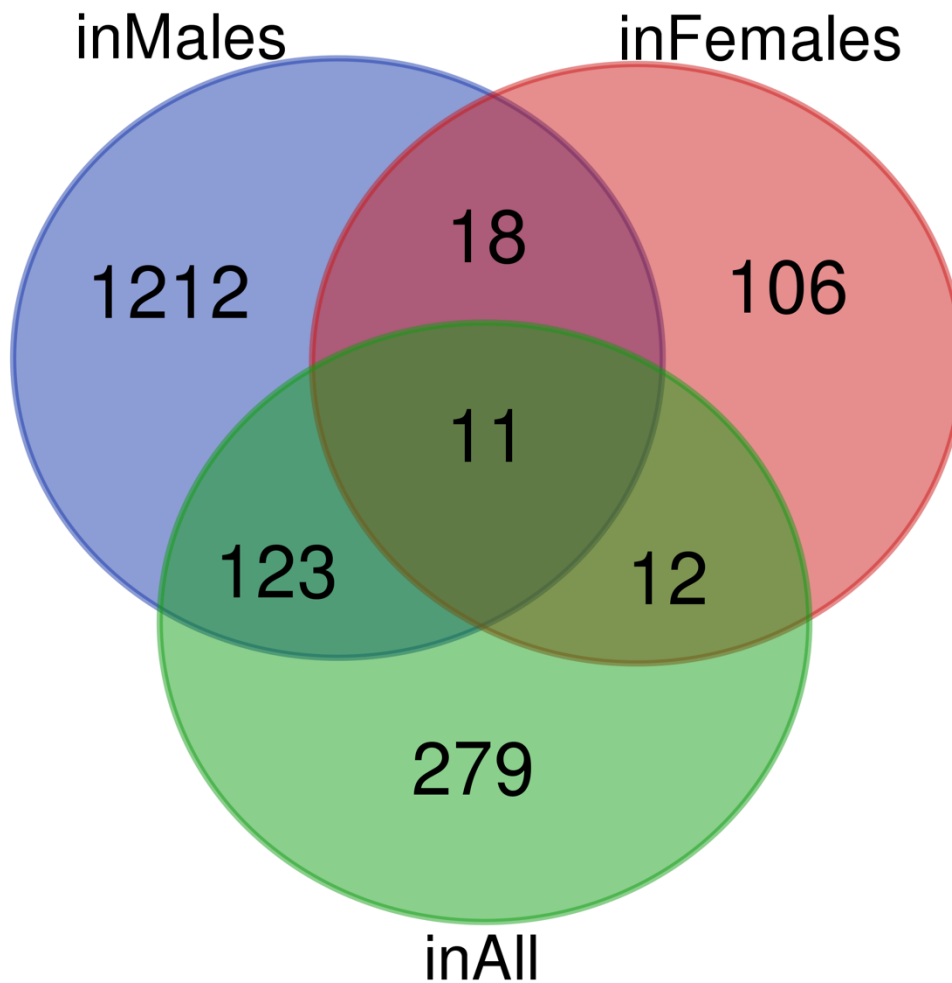


Figure S14. Overlaps between gene lists emerged from joined and sex-specific DMP analysis.

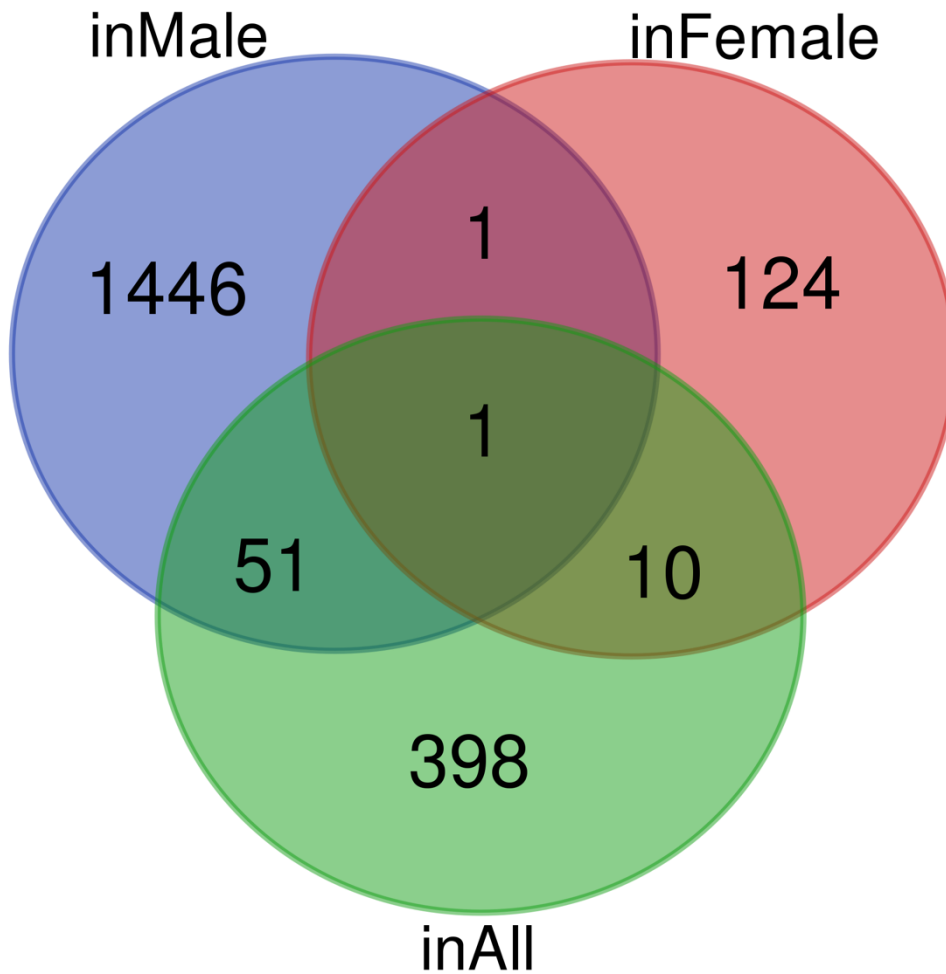


Figure S15. Overlaps between CpG sites lists emerged from joined and sex-specific DMP analysis.