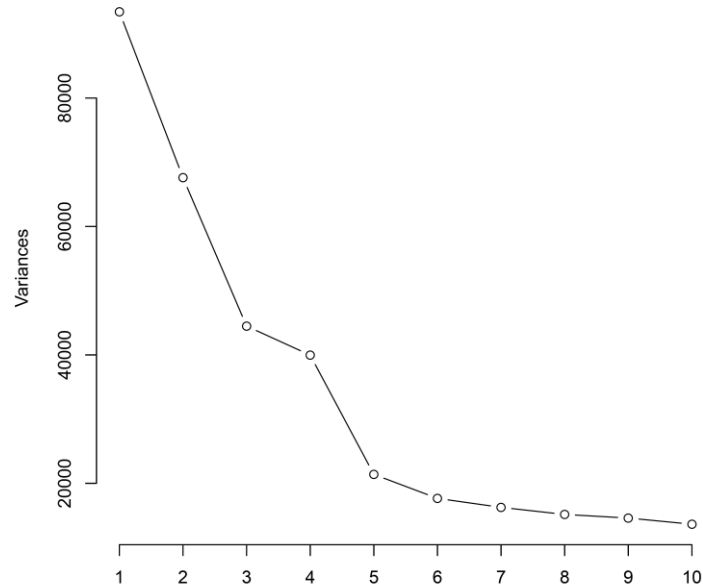
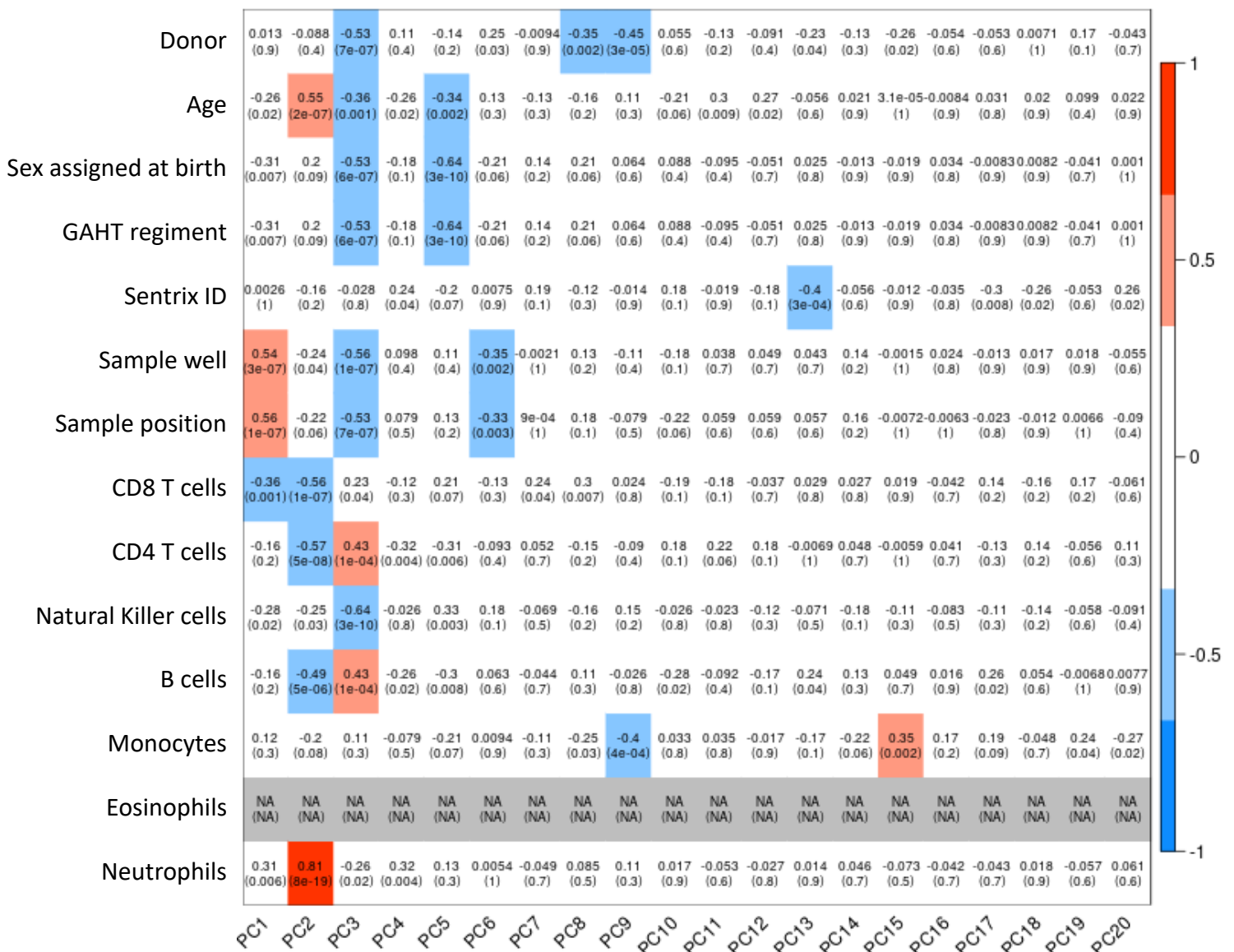


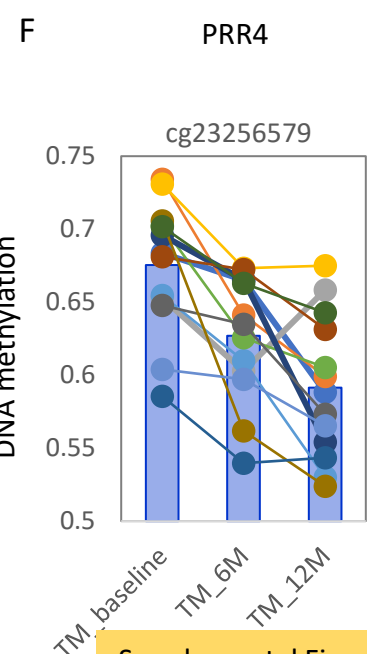
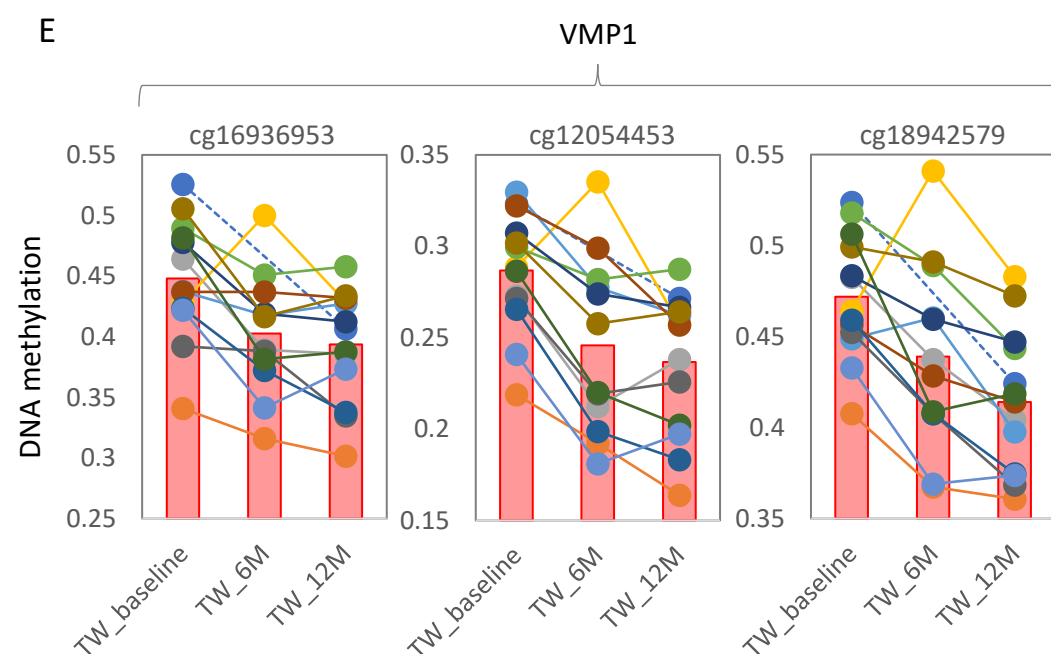
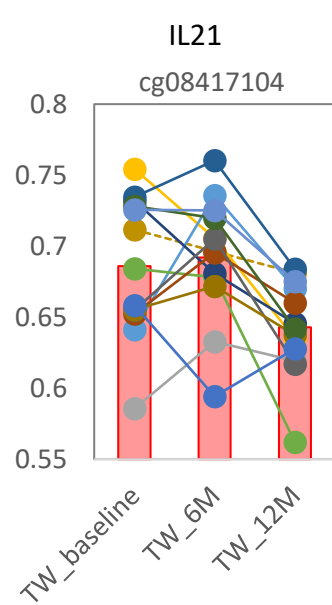
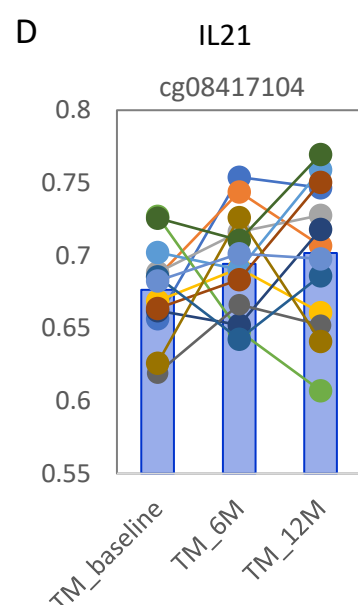
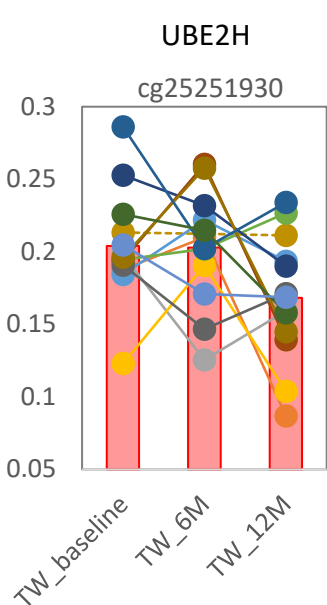
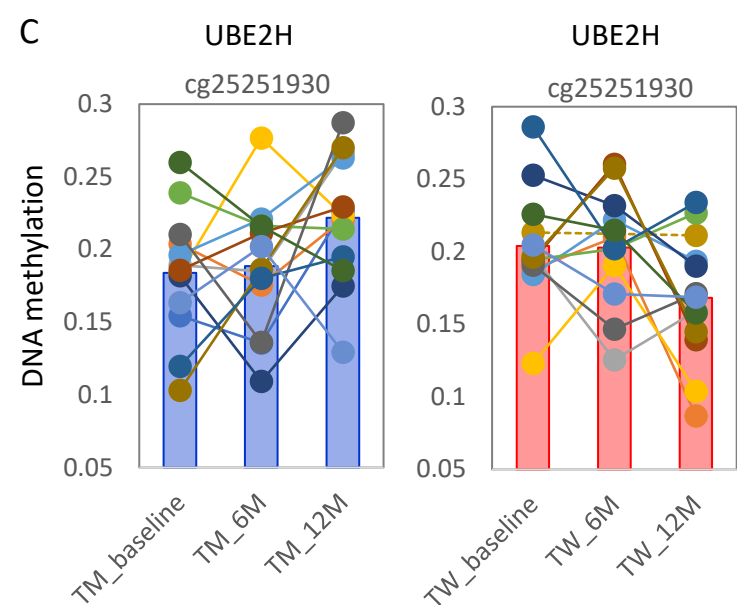
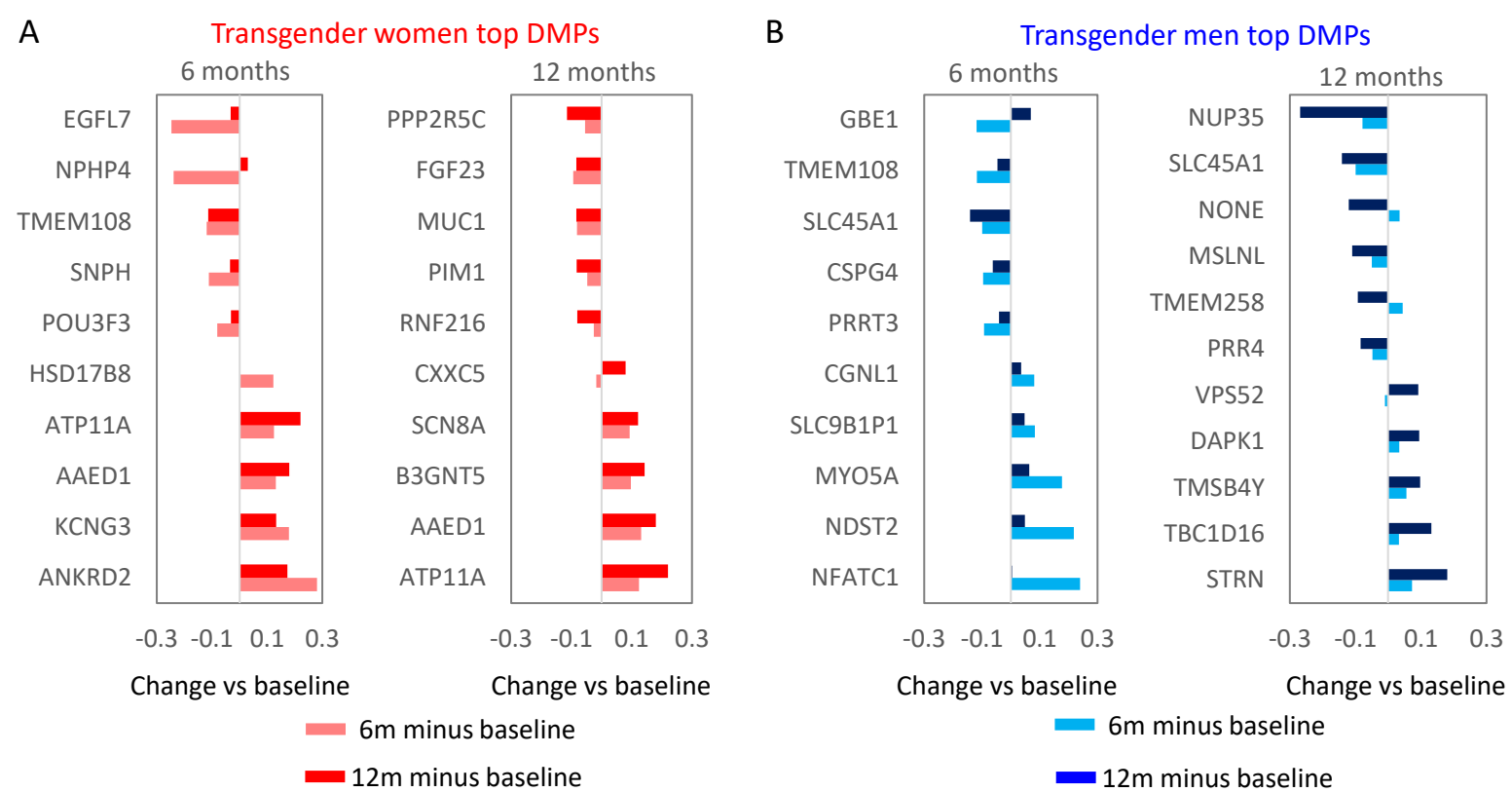
A

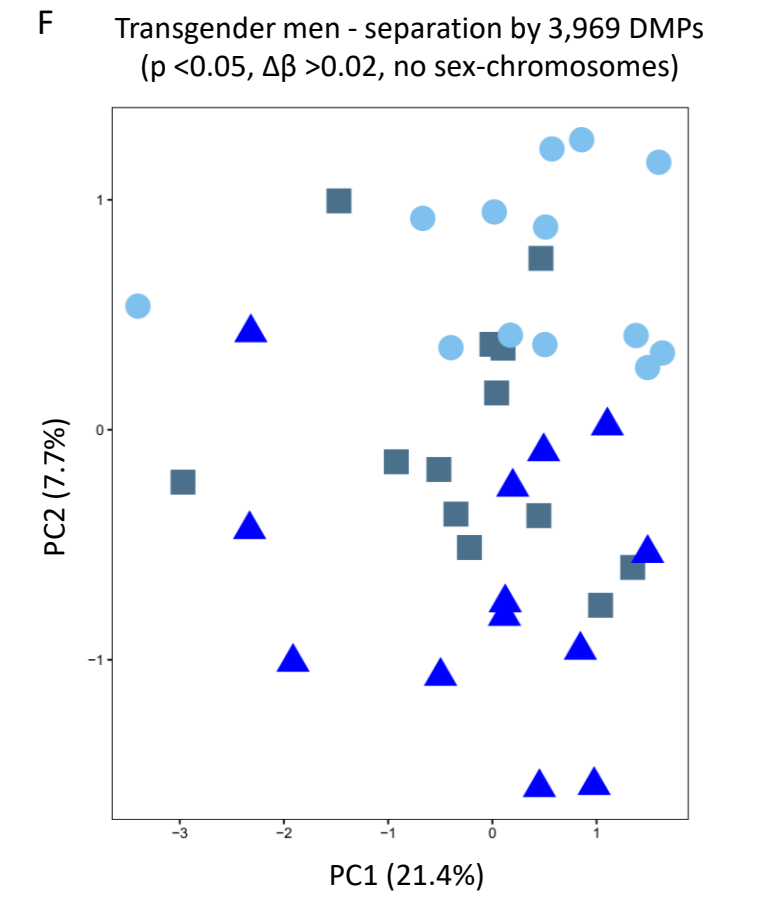
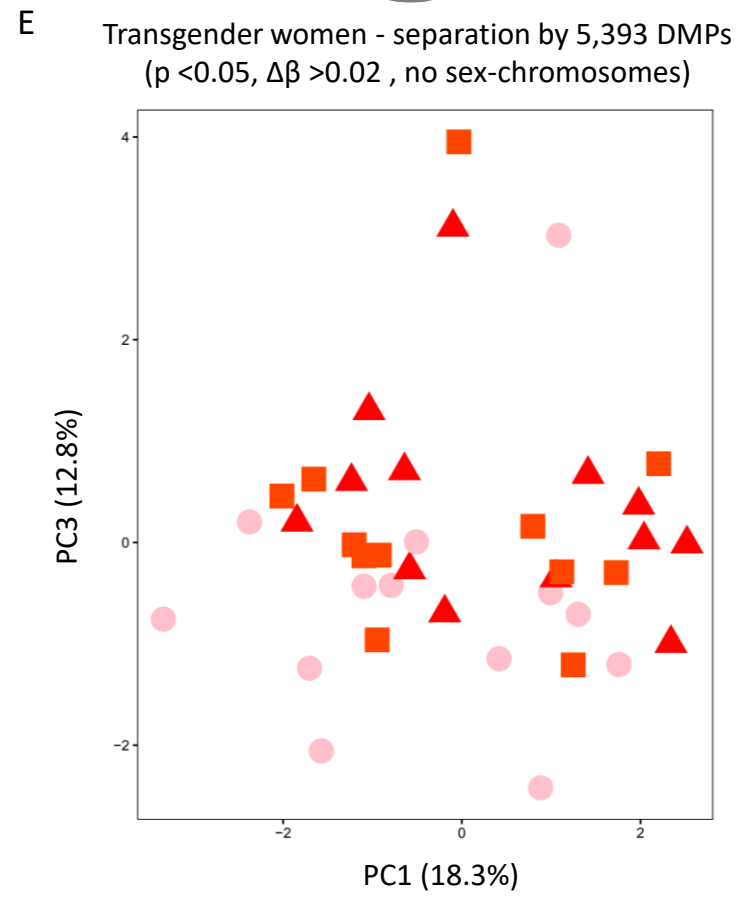
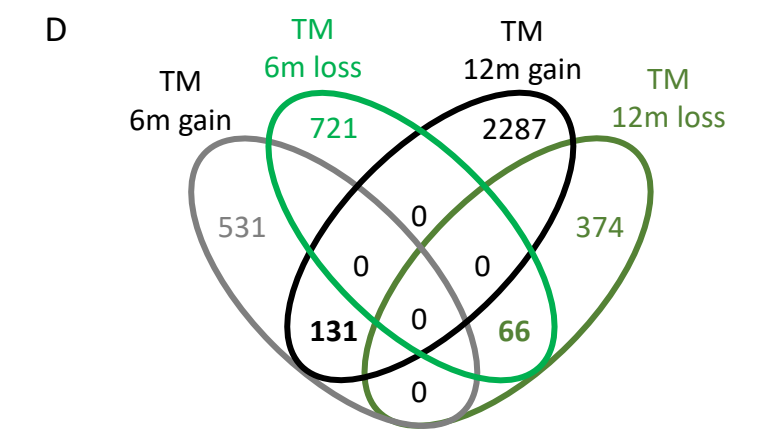
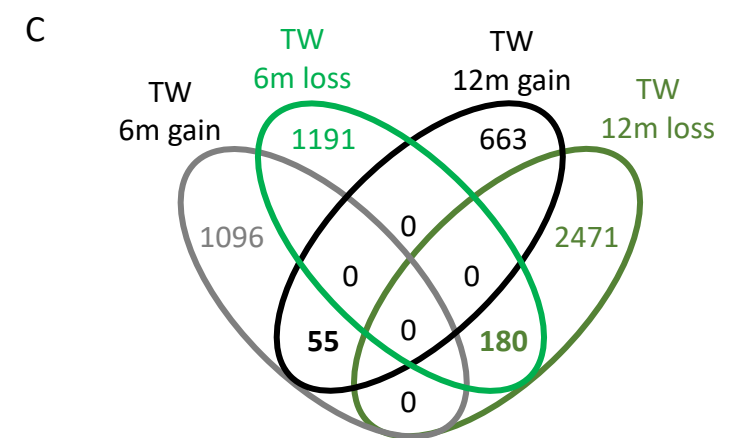
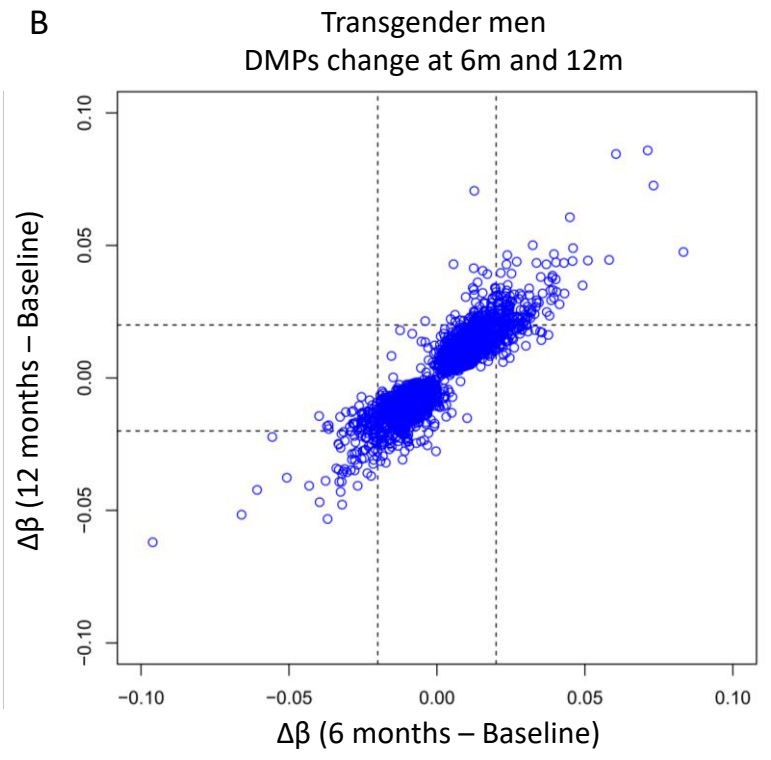
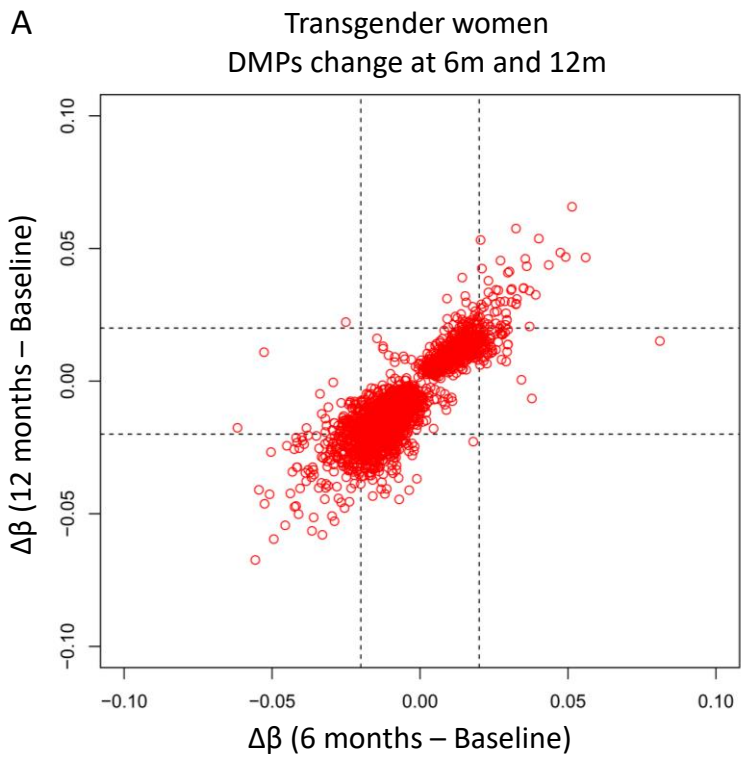
PCA plot of 1st 10 principal components



B

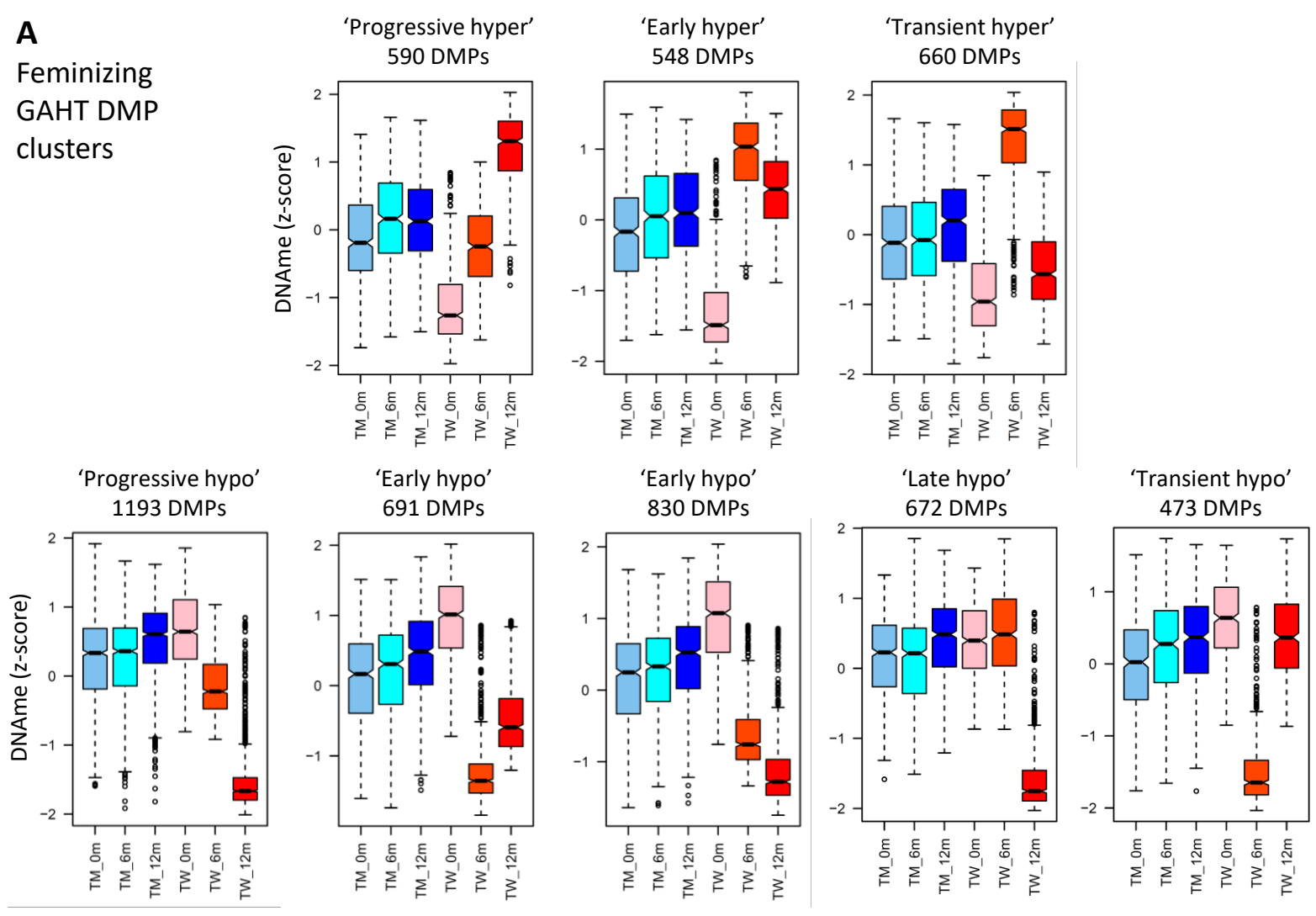
PCA – Confounders relationships
'correlation (p-value)'



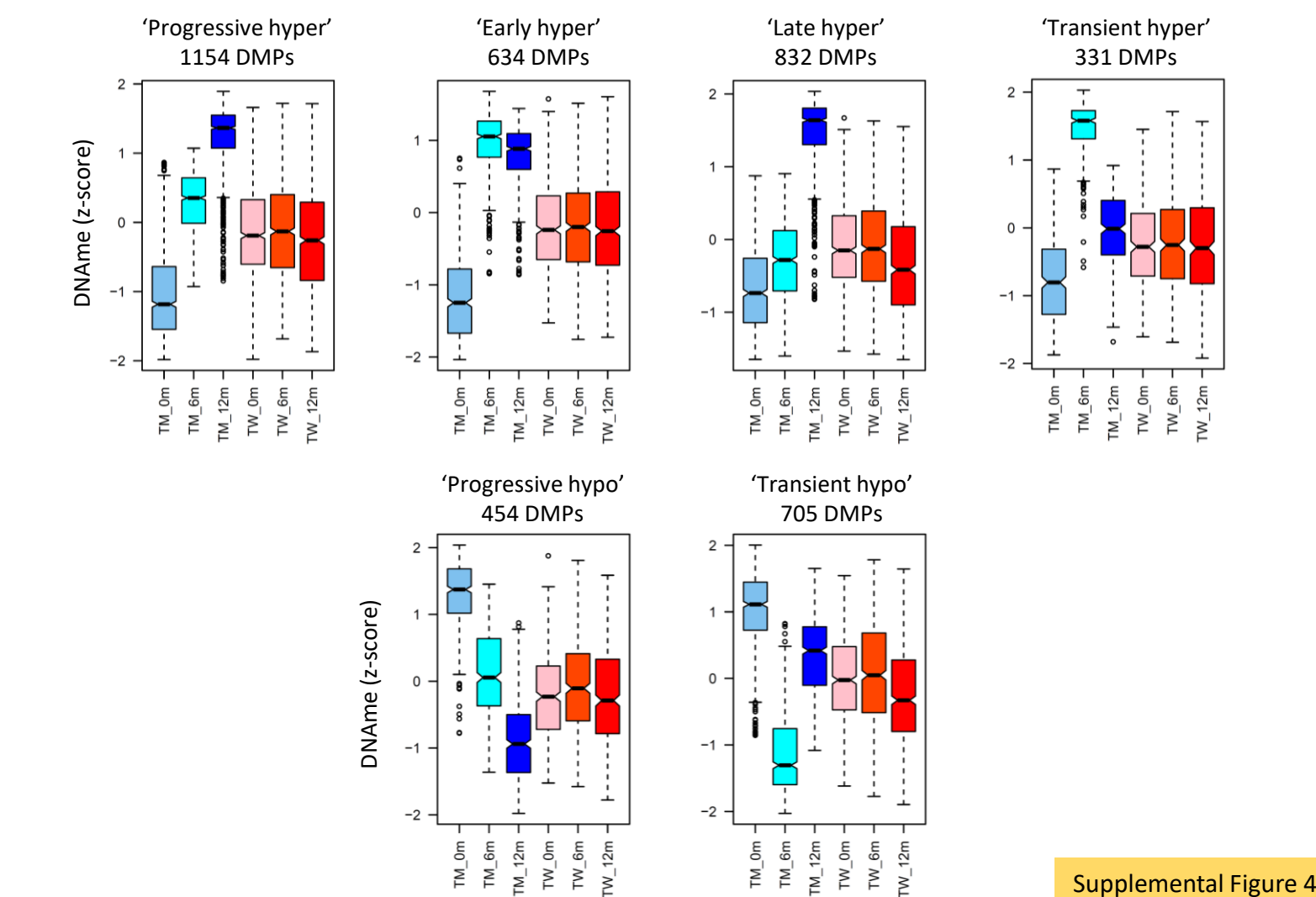


Transgender women: ● baseline, ■ 6 months, ▲ 12 months

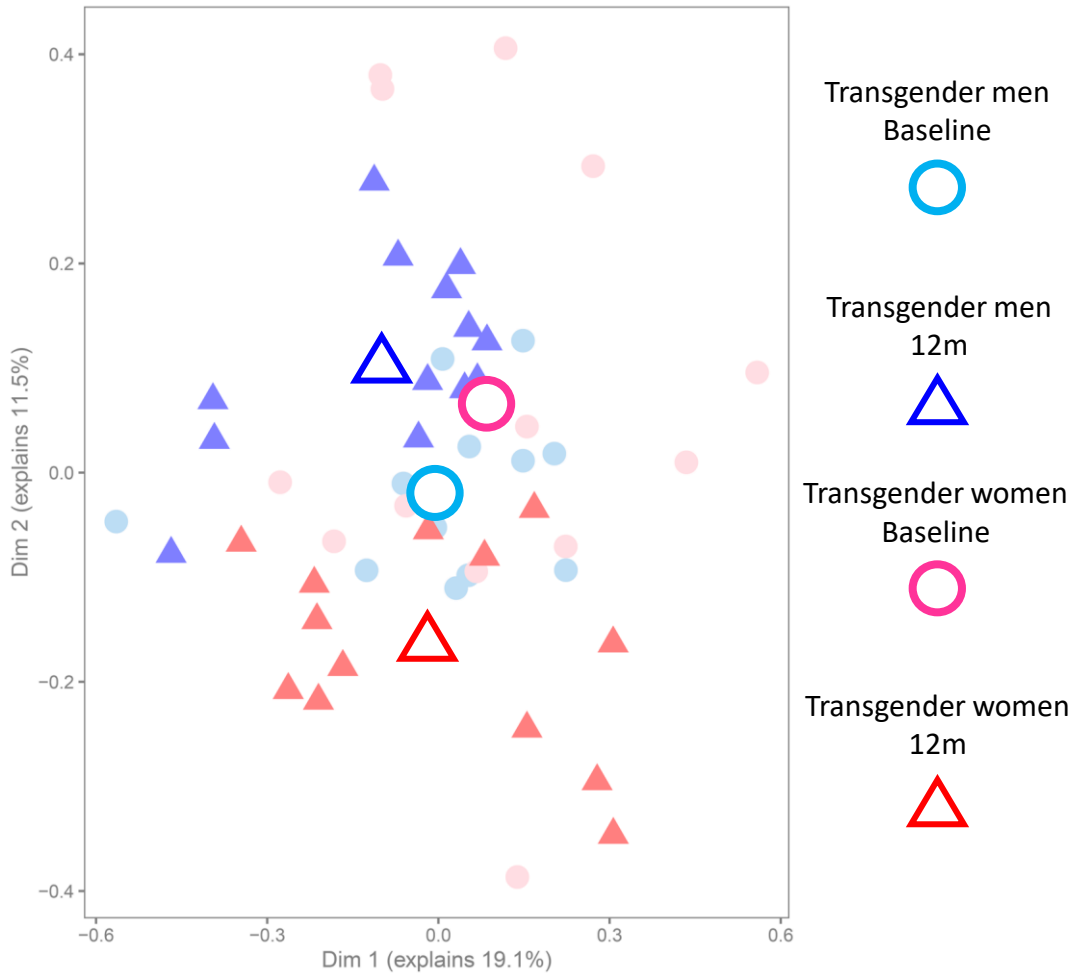
Transgender men: ● baseline, ■ 6 months, ▲ 12 months

AFeminizing
GAHT DMP
clusters**B**

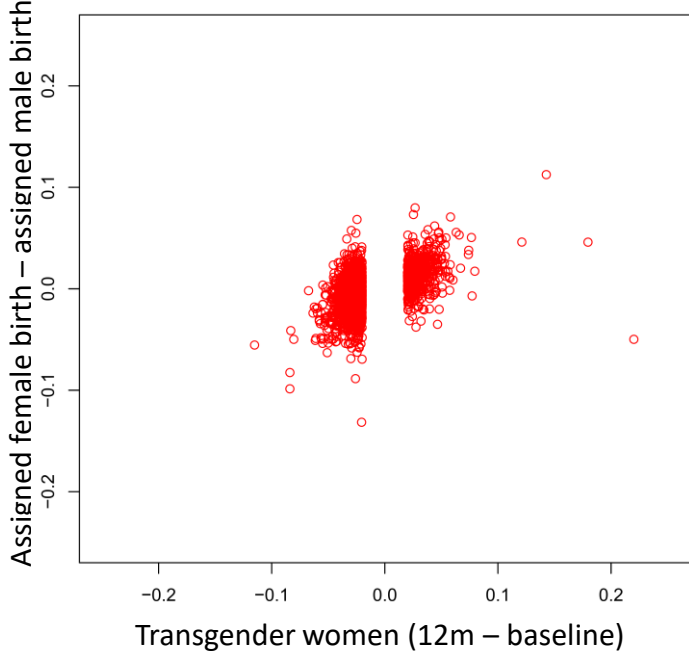
Masculinizing GAHT DMP clusters



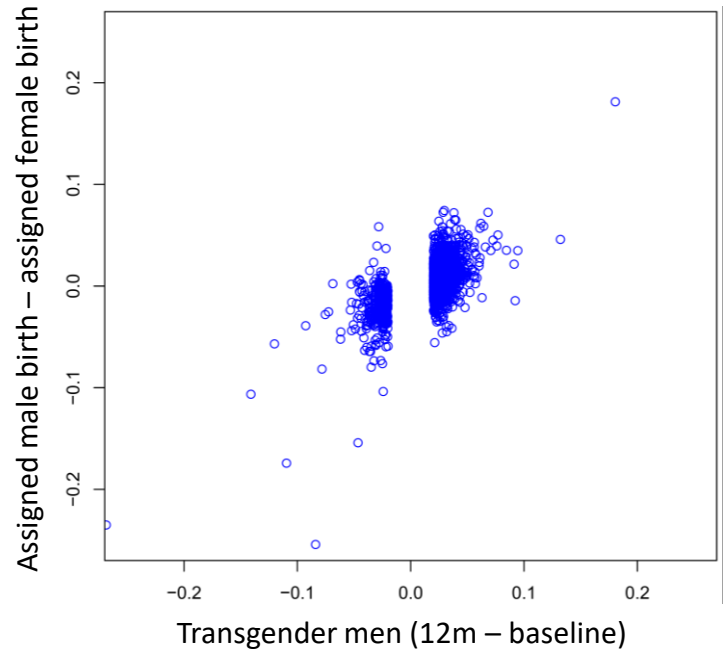
A Top probes in feminizing and/or masculinizing comparisons
(Means highlighted)



B Feminizing GAHT 12m DMPs ($p < 0.05$, $\Delta\beta > 0.02$)



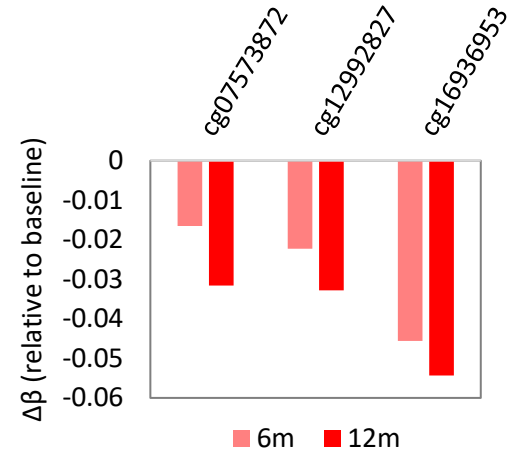
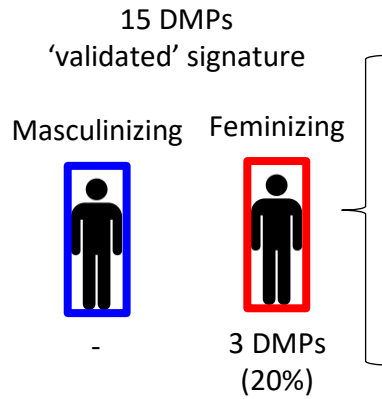
C Masculinizing GAHT 12m DMPs ($p < 0.05$, $\Delta\beta > 0.02$)



A Pregnancy-associated DMPs



Gruzieva et al. 2019



B Rheumatoid Arthritis

354 rheumatoid arthritis cases

vs

337 controls

Liu et al. 2013

Top 5,000 DMPs

Masculinizing



4 DMPs

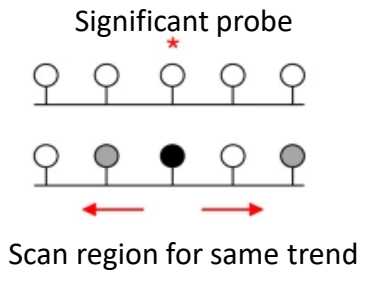
Feminizing



2 DMPs

~ 0.1%
Overlap

A Identifying DMRs



B

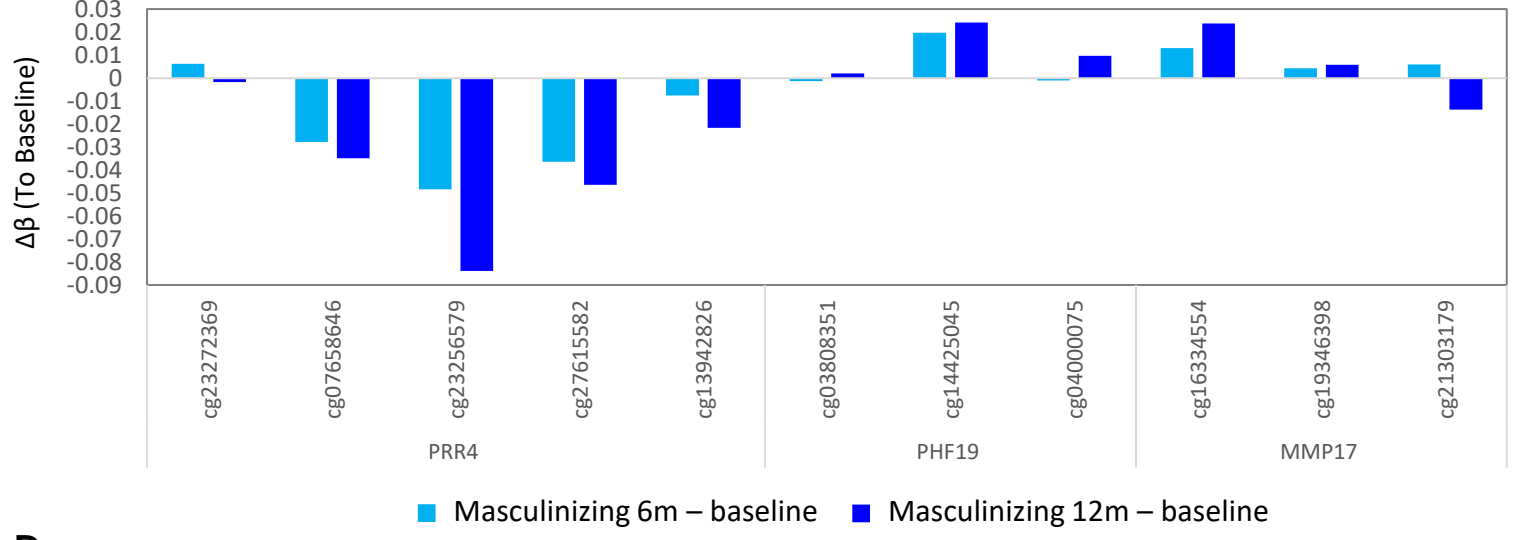
Feminizing GAHT (6 months v baseline):
6 DMRs: near *TAS1R2*, *ZFP36L1*, *RTL1*, *MED31*, *VMP1*, *SLC35D3*

Feminizing GAHT(12 months v baseline):
3 DMRs: near *CAT*, *LANCL3*, *HUS1*

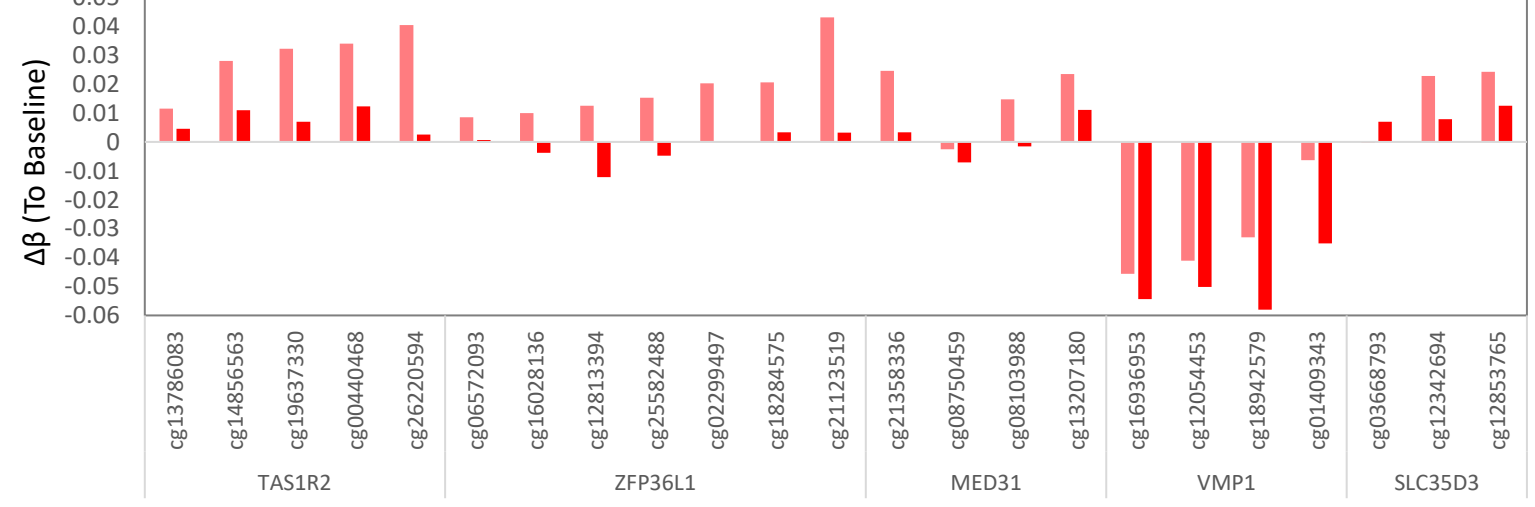
Masculinizing GAHT (6 months v baseline):
0 DMRs:

Masculinizing GAHT (12 months v baseline):
3 DMRs: near *PRR4*, *PHF19*, *MMP17*

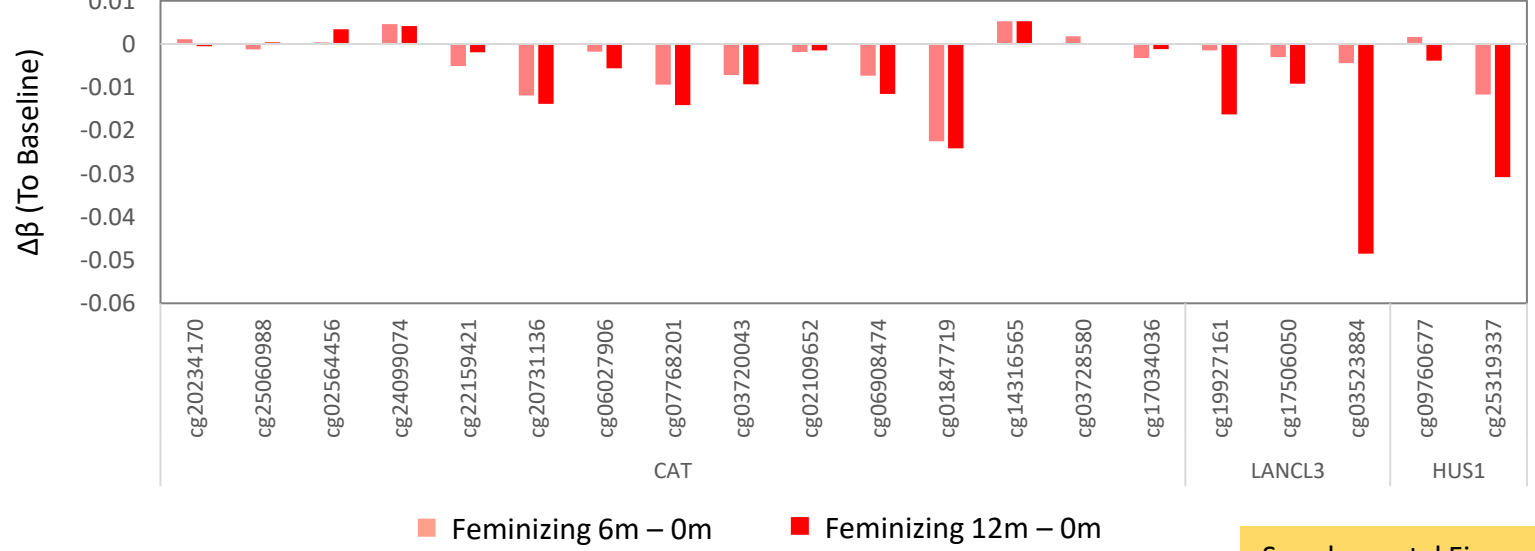
C Transgender men - 3 DMRs (12 months v baseline)



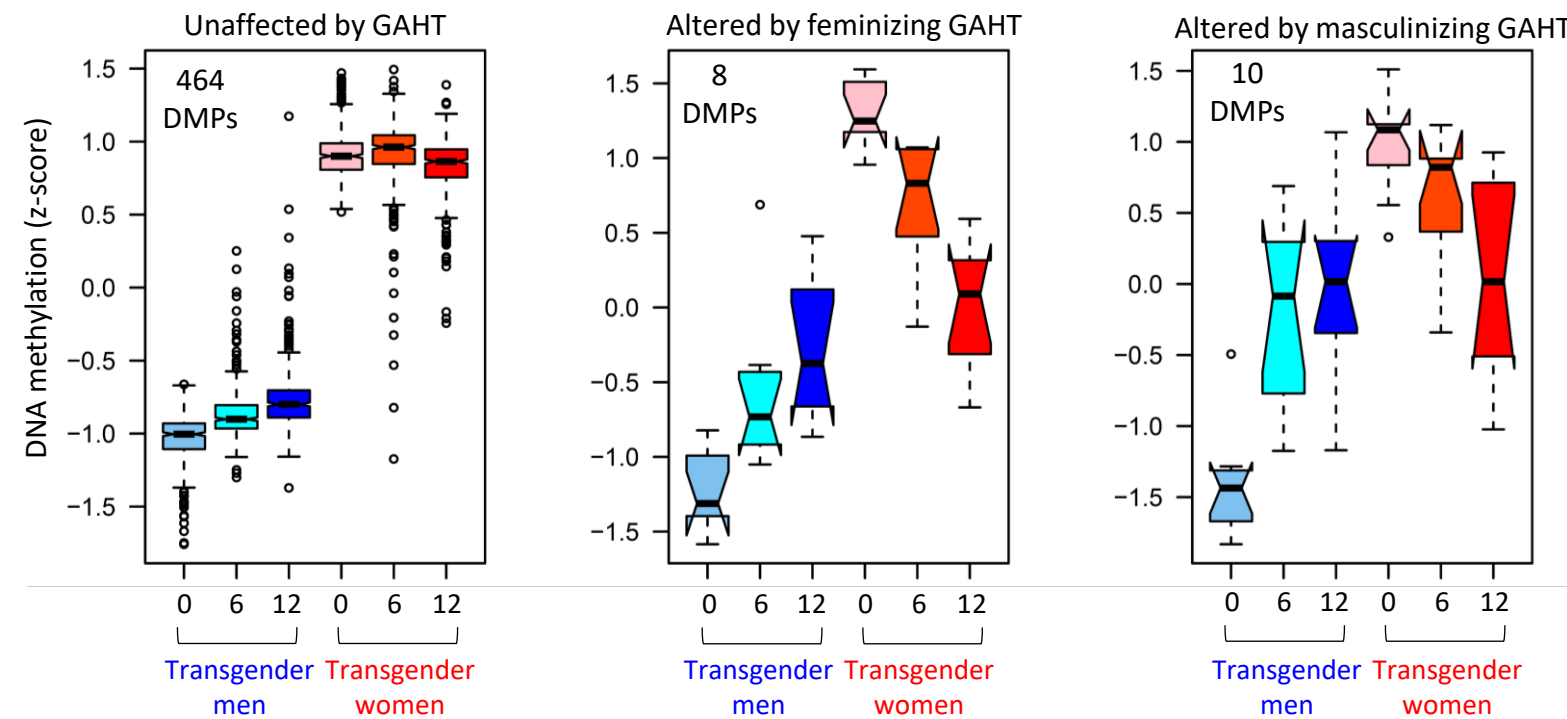
D Transgender women - 6 DMRs (6 months v baseline)



E Transgender women - 3 DMRs (12 months v baseline)



A Higher autosomal DNA methylation in assigned male at birth



B. X chromosome

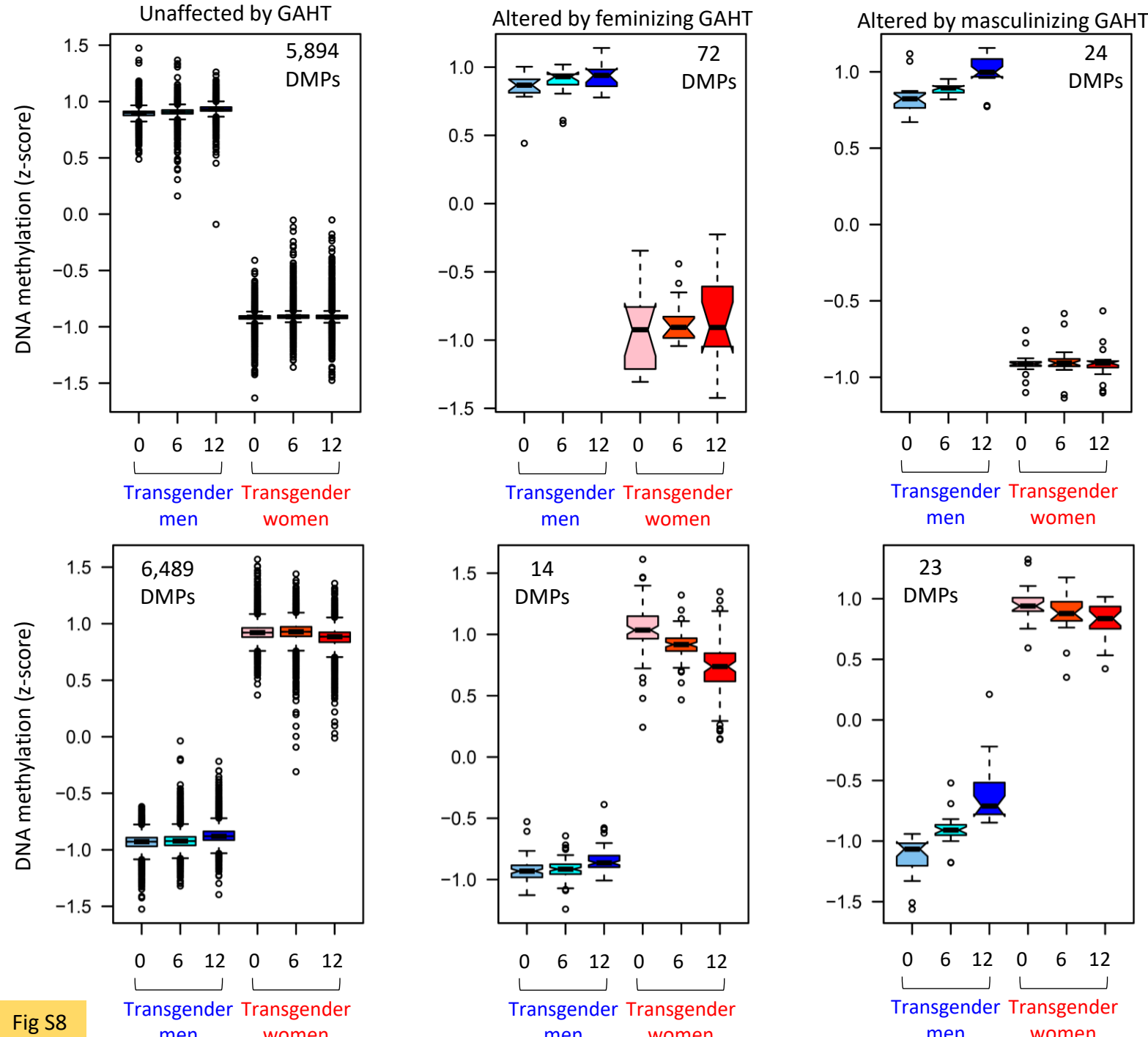


Fig S8

XIST promoter DNA methylation

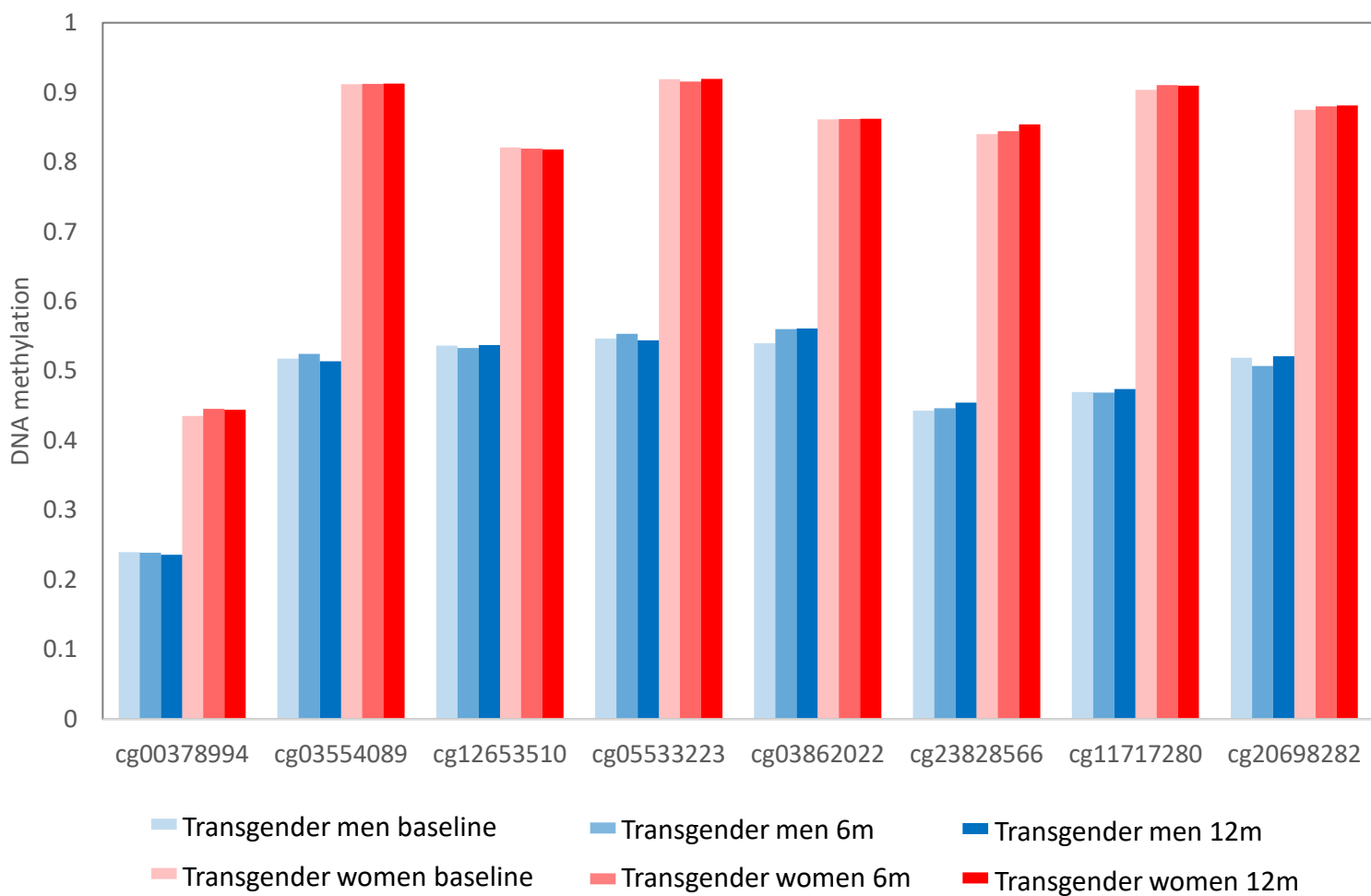
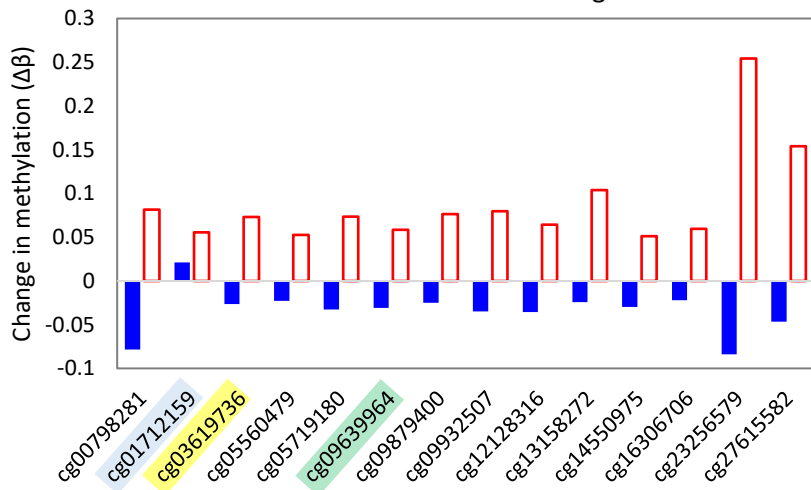
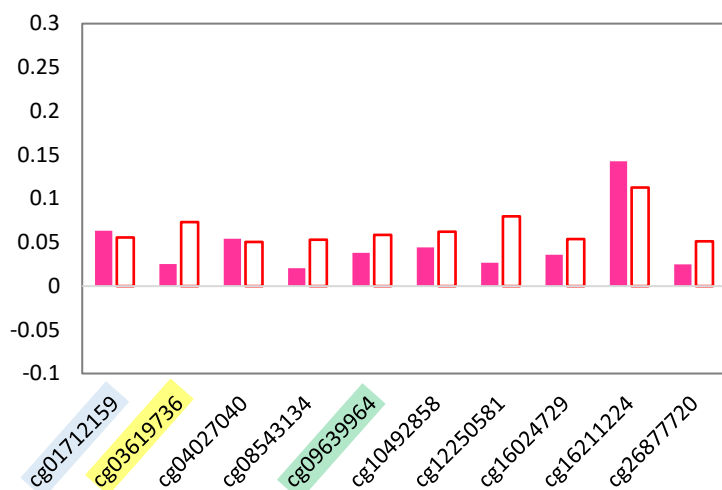


Figure S9

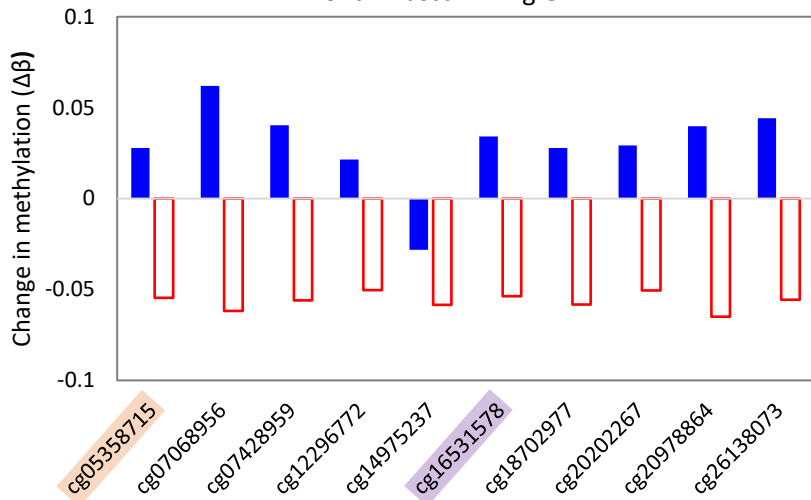
A Assigned female gain of methylation probes affected by 12-month masculinizing GAHT



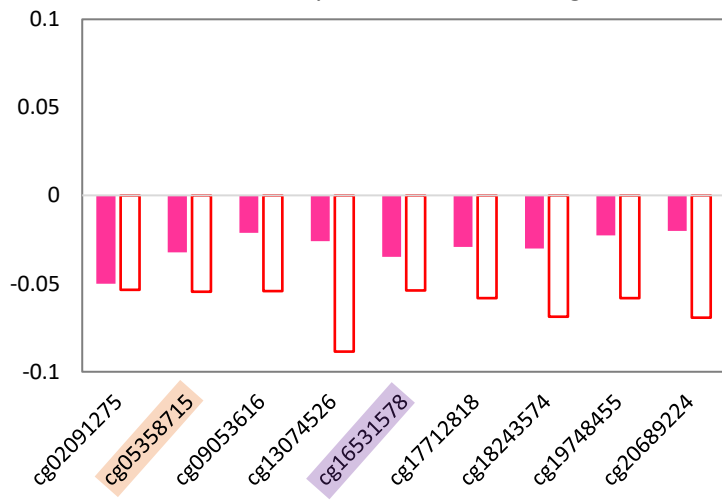
B Assigned female gain of methylation probes affected by 12-month feminizing GAHT



C Assigned female loss of methylation affected by 12-month masculinizing GAHT



D Assigned female loss of methylation probes affected by 12-month feminizing GAHT



■ Masculinizing 12m - 0m ■ Feminizing 12m - 0m
□ Baseline Transgender men - Baseline Transgender women

<i>CHMP1A</i> (-45)
<i>ACACB</i> (+368)
<i>CBFA2T3</i> (+48872)
<i>TIMM22</i> (+8944)
<i>TRERF1</i> (+49685)