

Supplementary Table 1: Datasets included in this study. Included Full Term Analysis: Y/N variable indicating if samples from dataset were used in full term analysis. Inclusion Criteria Full Term Analysis: criteria to select samples for full term analysis. Included Early Term Analysis: Y/N variable indicating if samples from dataset were used in any of the trimester specific analyses. Inclusion Criteria Early Term Analysis: criteria to select samples for inclusion in trimester specific cohorts. N_Term/1stTerm/2ndTerm/3rdTerm: Number of samples (pre QC) included from dataset in each analysis subgroup.

GEOID	Included Full Term Analysis	Inclusion Criteria Full Term Analysis	Included Early Term Analysis	Inclusion Criteria Early Term Analysis	N term	N 1stTerm	N 2ndTerm	N 3rdTerm
GSE108567	Y	Via Gestational Age	Y	Via Gestational Age	45	NA	NA	14
GSE100197	Y	Term control	Y	Preterm control	19	NA	2	22
GSE98224	Y	Term control, AGA	Y	Preterm, control, AGA	9	NA	NA	5
GSE106089	N	NA	Y	All	NA	NA	46	NA
GSE103413	N	NA	Y	Chorionic villus	NA	NA	2	NA
GSE98938	Y	chorion, trophoblast, villi	Y	chorion, villi, trophoblast	6	NA	6	NA
GSE93208	N	NA	Y	All	NA	19	NA	NA
GSE71719	Y	Bisulfite converted	N	NA	23	NA	NA	NA
GSE71678	Y	All	N	NA	323	NA	NA	NA
GSE75248	Y	AGA samples	N	NA	174	NA	NA	NA
GSE75196	Y	Healthy	N	NA	16	NA	NA	NA
GSE69502	N	NA	Y	Chorionic Villi, Controls	NA	NA	16	NA
GSE74738	Y	Controls	N	NA	22	NA	NA	NA
GSE66210	N	NA	N	Chorionic villus, normal	NA	14	NA	NA
				SUM	637	33	72	41

Supplementary Figures

Supplementary Figure 1: PCA plot of 3rd Trimester placenta samples before and after batch effect correction.

Top triangle shows principal components generated from methylation M-values at all autosomal probes passing QC prior to quantile normalization or surrogate variable analysis. Bottom triangle shows residuals of quantile normalized autosomal M-values regressed onto estimated surrogate variables.

Supplementary Figure 2: PCA plot of 2nd Trimester placenta samples before and after batch effect correction.

Top triangle shows principal components generated from methylation M-values at all autosomal probes passing QC prior to quantile normalization or surrogate variable analysis. Bottom triangle shows residuals of quantile normalized autosomal M-values regressed onto estimated surrogate variables.

Supplementary Figure 3: PCA plot of 1st Trimester placenta samples before and after batch effect correction.

Top triangle shows principal components generated from methylation M-values at all autosomal probes passing QC prior to quantile normalization or surrogate variable analysis. Bottom triangle shows residuals of quantile normalized autosomal M-values regressed onto estimated surrogate variables.

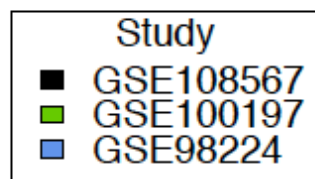
Supplementary Figure 4: Distribution of absolute value of mean differences in sites that do discriminate placenta cell types (gray, n = 1,285) and sites that do not (orange, n = 3927), among the genome-wide significant sites from the full term analysis. Cell type discriminating probes determined by Yuan et al.

Supplementary Figure 5: Manhattan plots showing single site association results for each early term analysis.

Supplementary Figure 6: Volcano plot for full term DMR analysis. The x-axis measures the average methylation difference between male and female fetuses, and the y-axis measures the size of the DMR in base pairs. The blue points represent DMRs considered significant ($\text{fwerArea} < 0.1$)

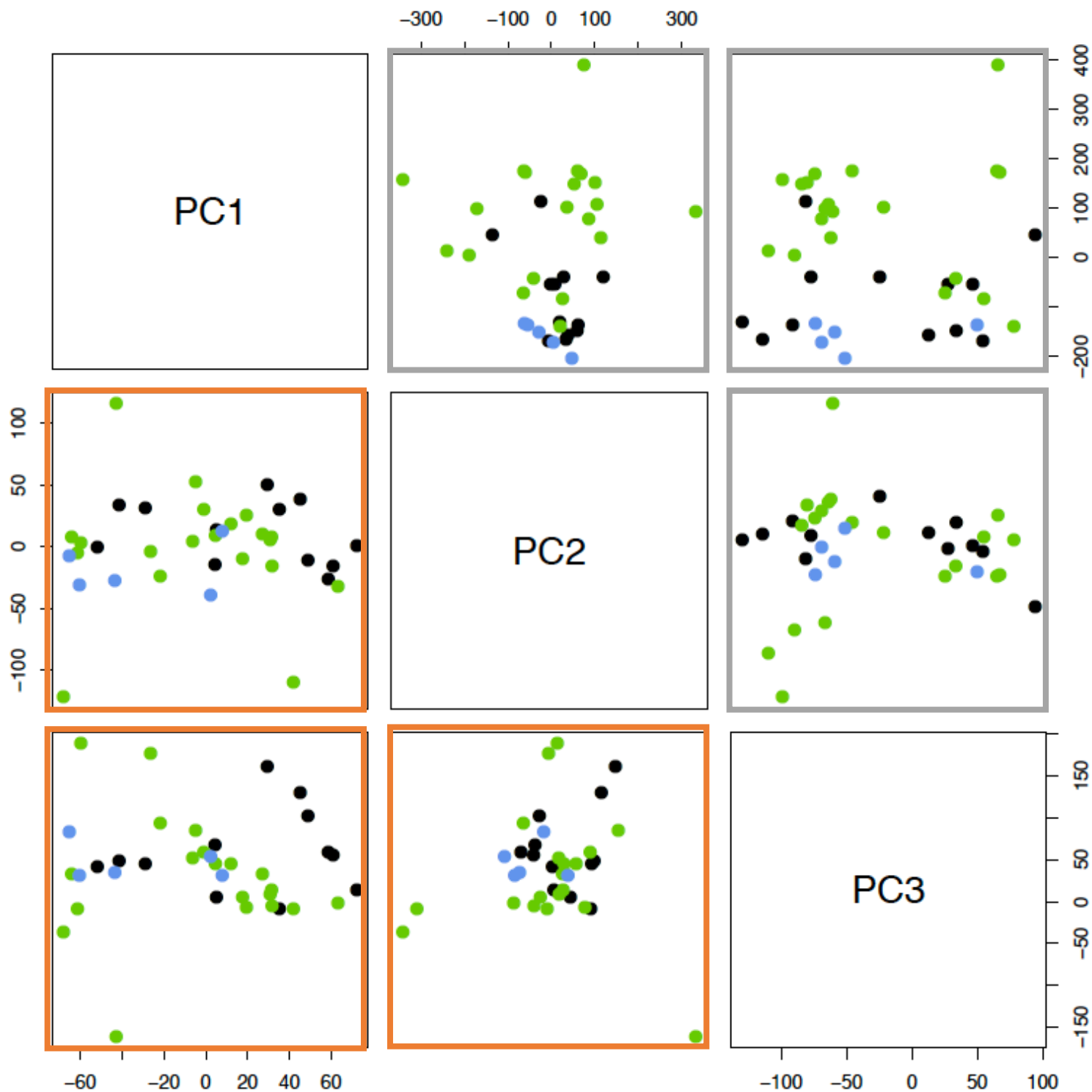
Supplementary Figures 7 - 14: Additional plots depicting significant DMRs from full term analysis across all gestational periods. Remaining DMRs exceeding fwerArea threshold of 0.1 as seen in Table 4 (excluding top-ranked DMR in ZNF175 promoter, see Figure 4). In each figure, DMRs are plotted as percent methylation as a function of genomic position. Dots indicate samples and solid lines indicate smooth lines through male sample values (blue) and female sample values (gold). Actual identified DMR region indicated via dashed lines. **a** Full Term Samples. **b** 1st Trimester Samples **c** 2nd Trimester Samples **d** 3rd Trimester Samples.

Supplementary Figures 15 - 18: Exploration of cell type heterogeneity in additional DMRs. Remaining DMRs containing cell type discriminating probes as determined by Yuan et al (see Table 4). DMRs are plotted as percent methylation as a function of genomic position. Dots indicate samples and solid lines indicate smooth lines through male sample values (blue) and female sample values (gold). Actual identified DMR region indicated via dashed lines. **a** DMR identified in full term analysis, plotted using full term samples from present study. **b - d** The same region, but plotted using samples from different datasets. **b** Term samples and individual placenta cell types from Yuan et al. **c** 1st Trimester samples from present study. **d** 1st trimester samples and individual placenta cell types from Yuan et al. In **b + d**, fractions indicate the proportion of probes in the region that were annotated by Yuan et al. as distinguishing that cell type in full term and 1st trimester samples, respectively. Villi samples were not evaluated in this manner by Yuan et al. as this is the unsorted bulk tissue.



Pre batch correction

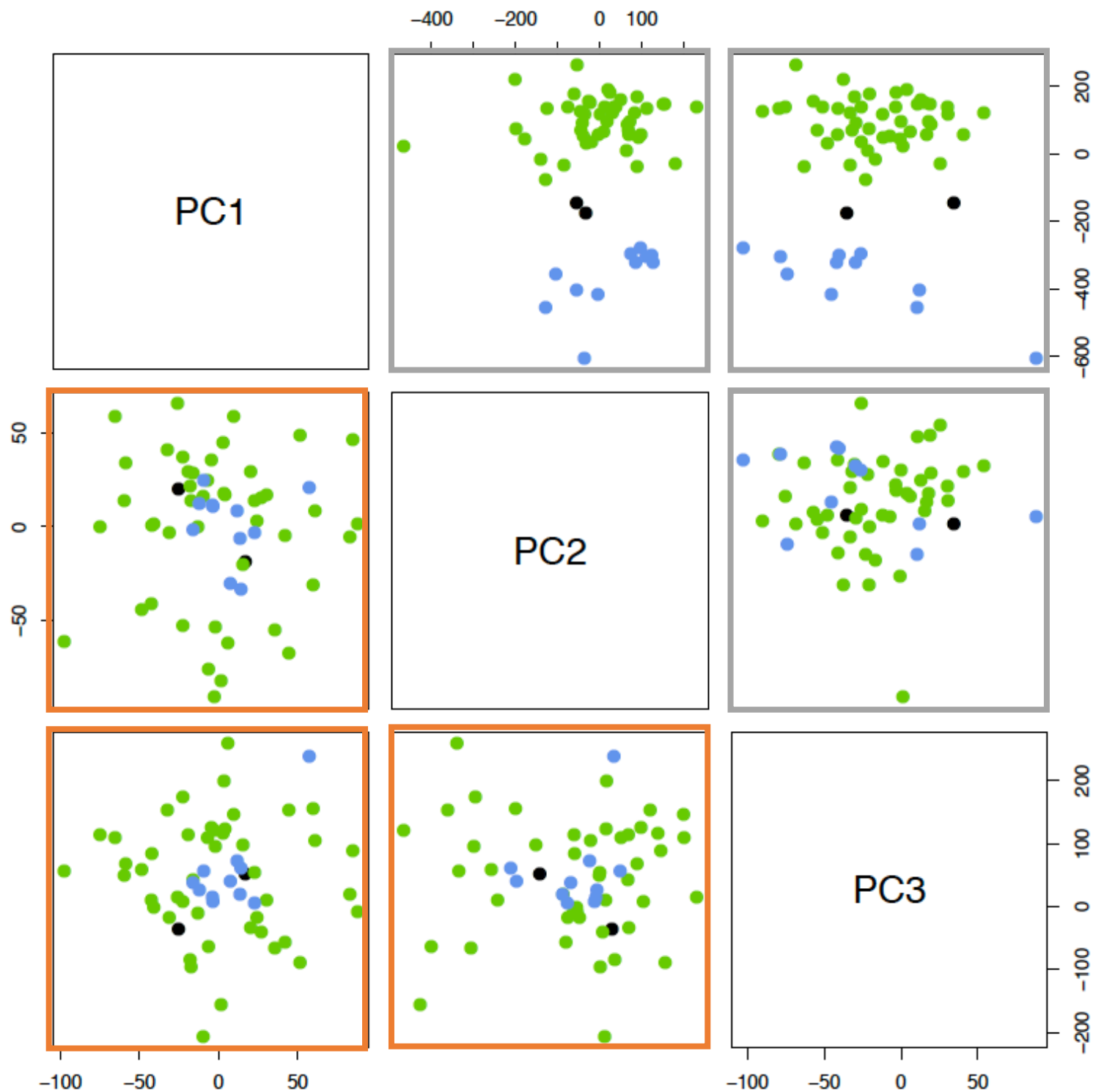
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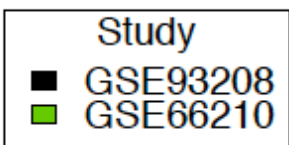


- GSE100197
- GSE106089
- GSE69502

Pre batch correction

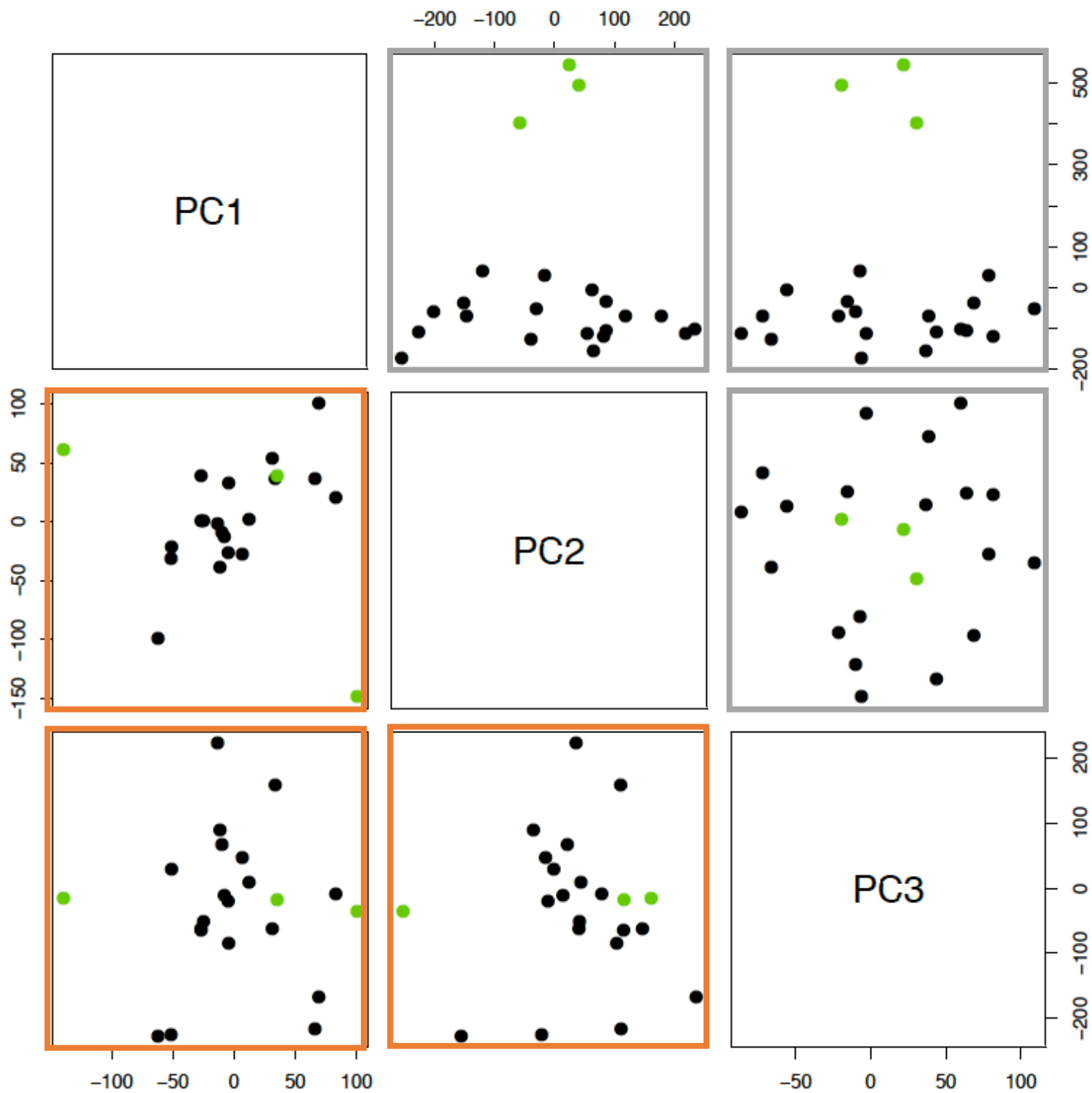
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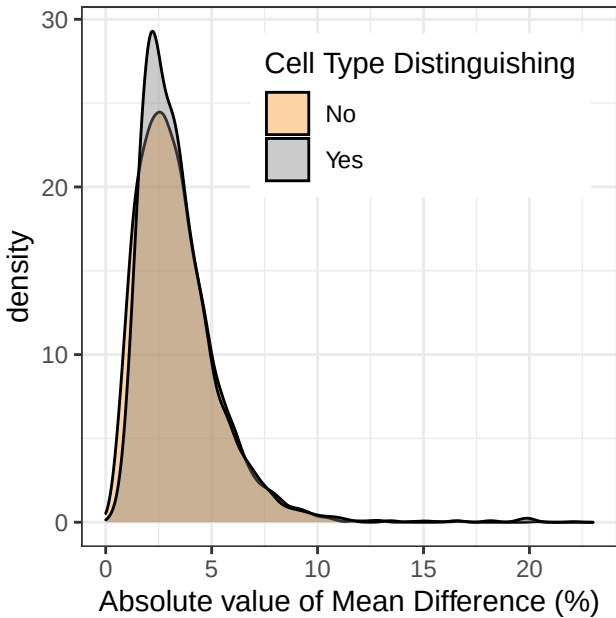


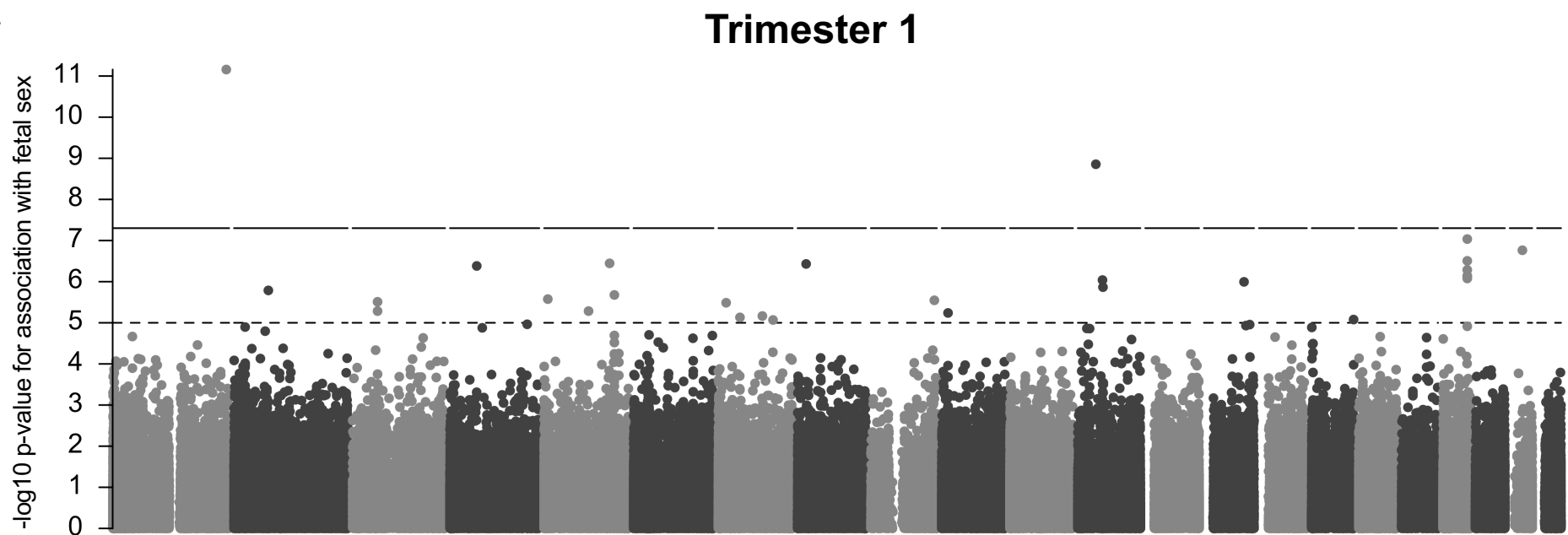
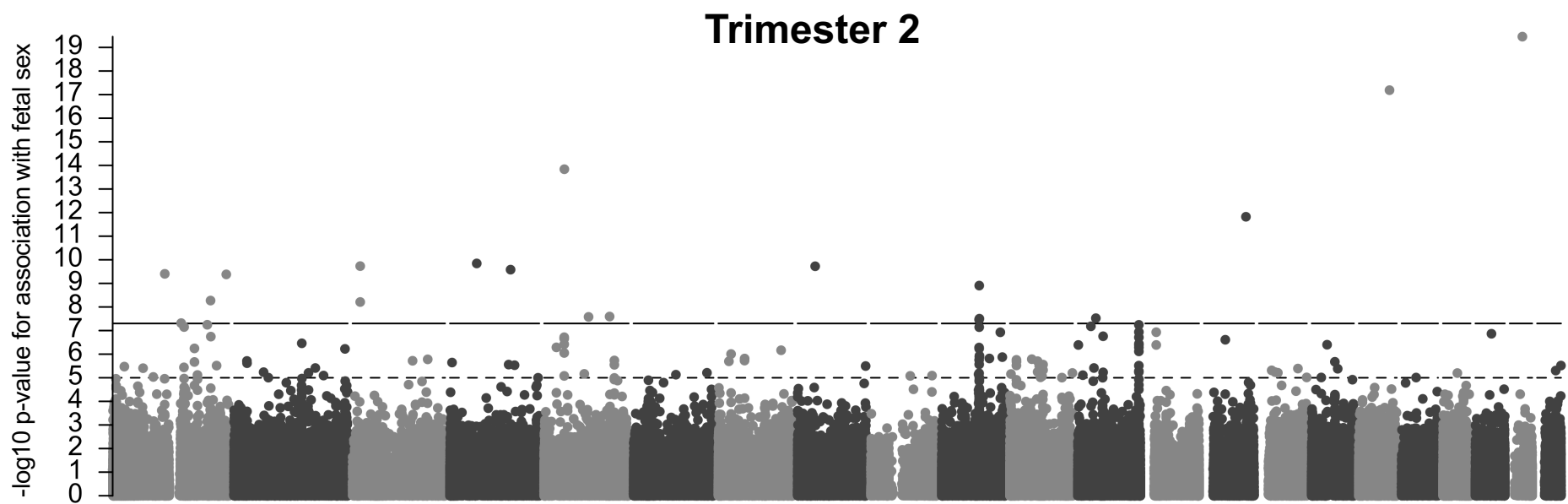
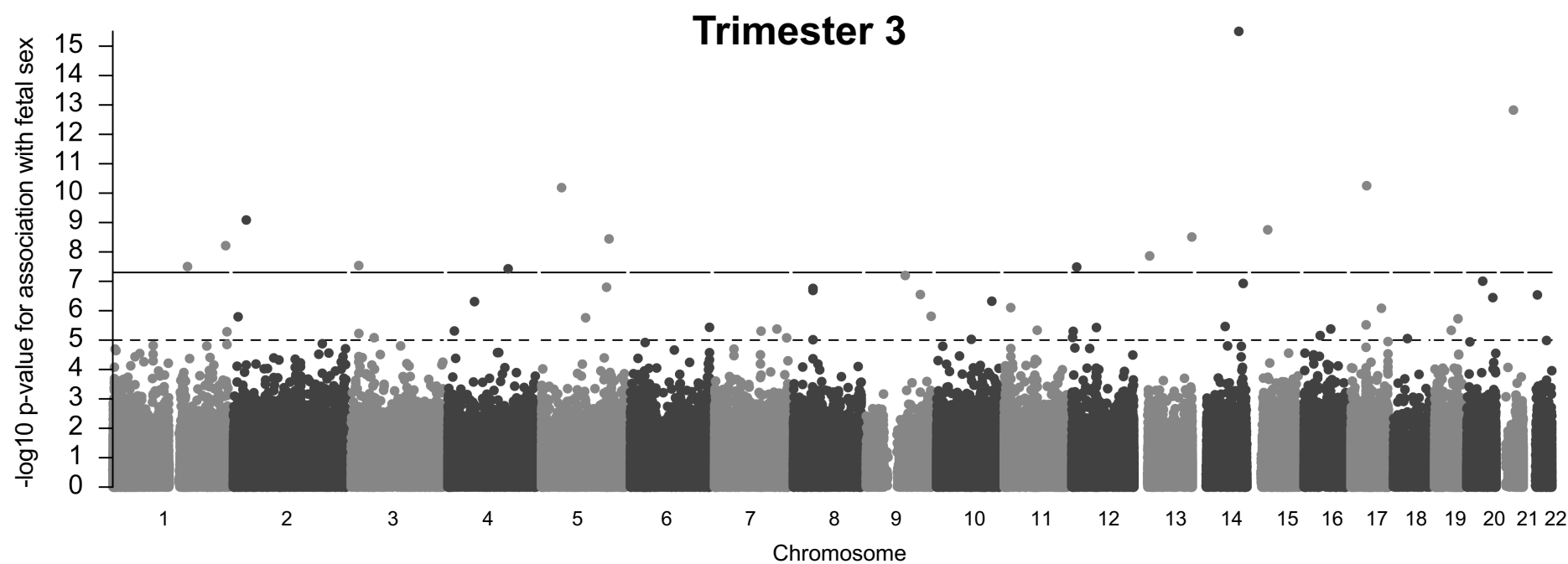


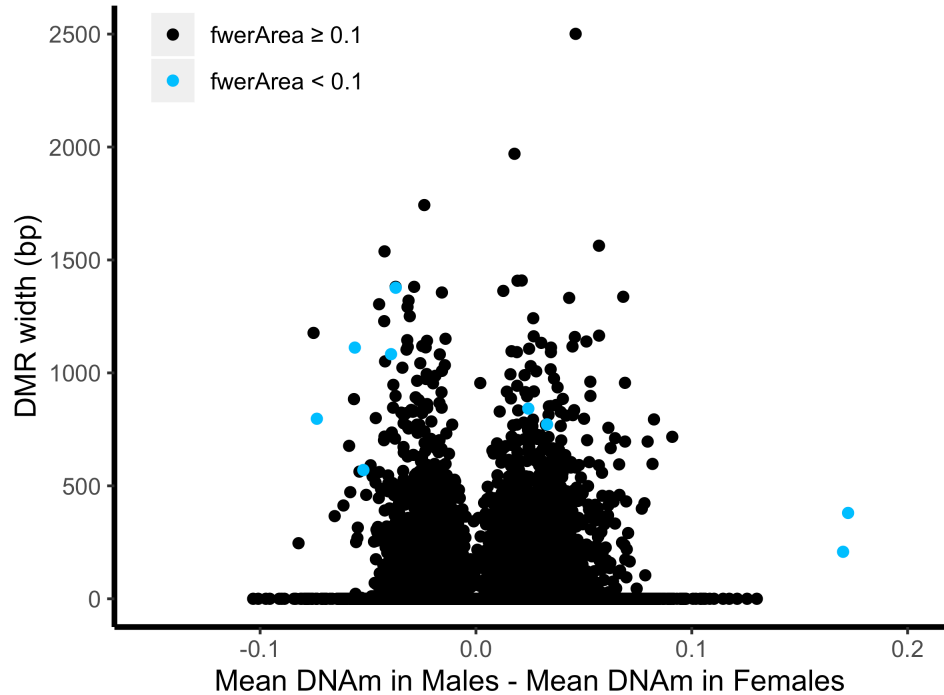
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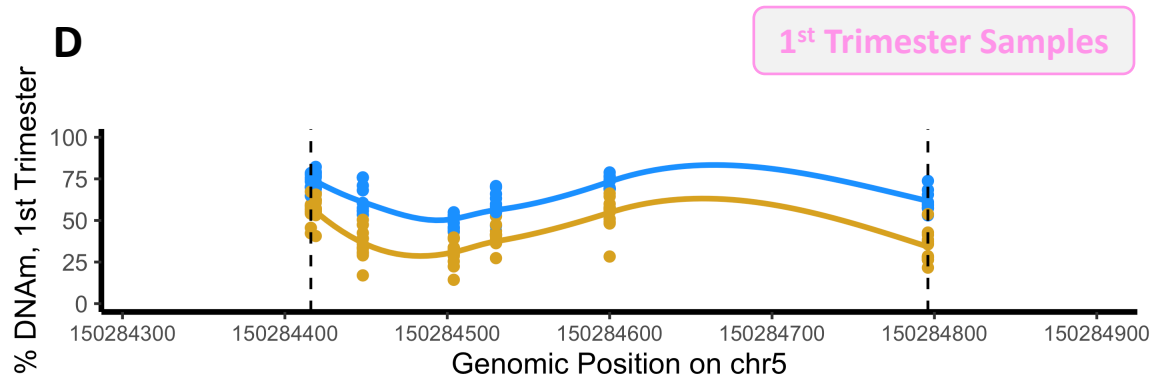
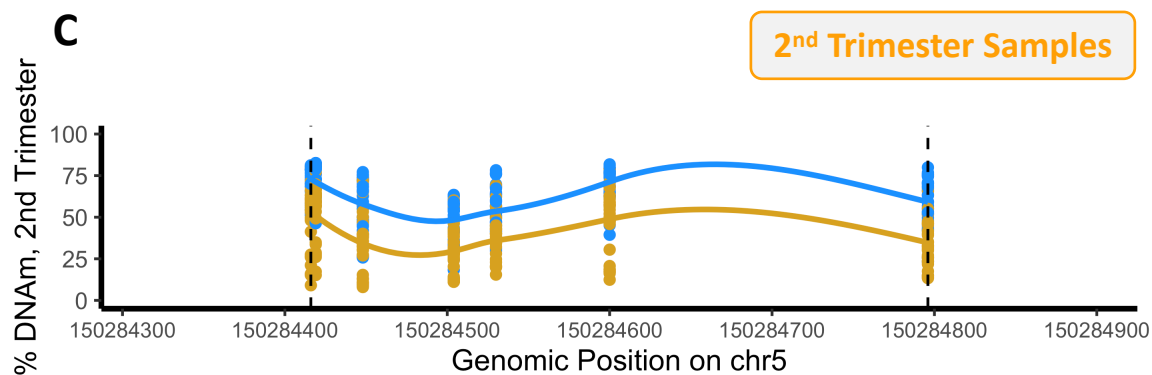
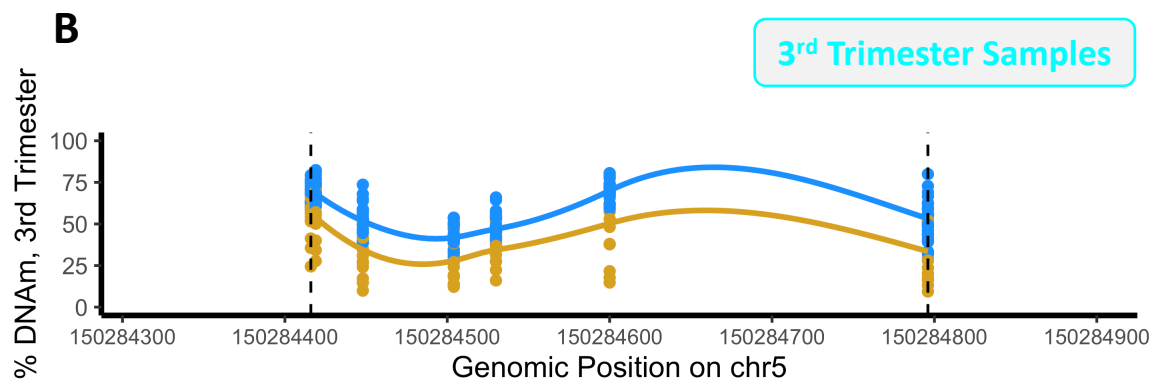
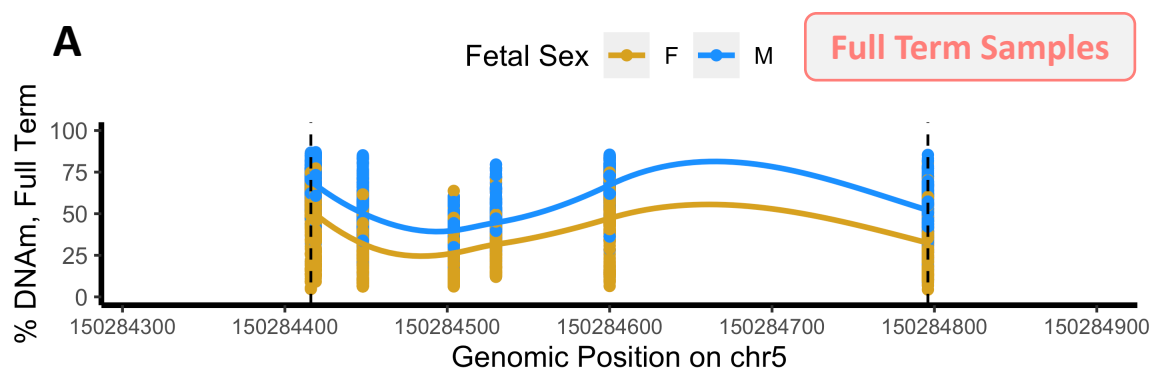
Post batch correction





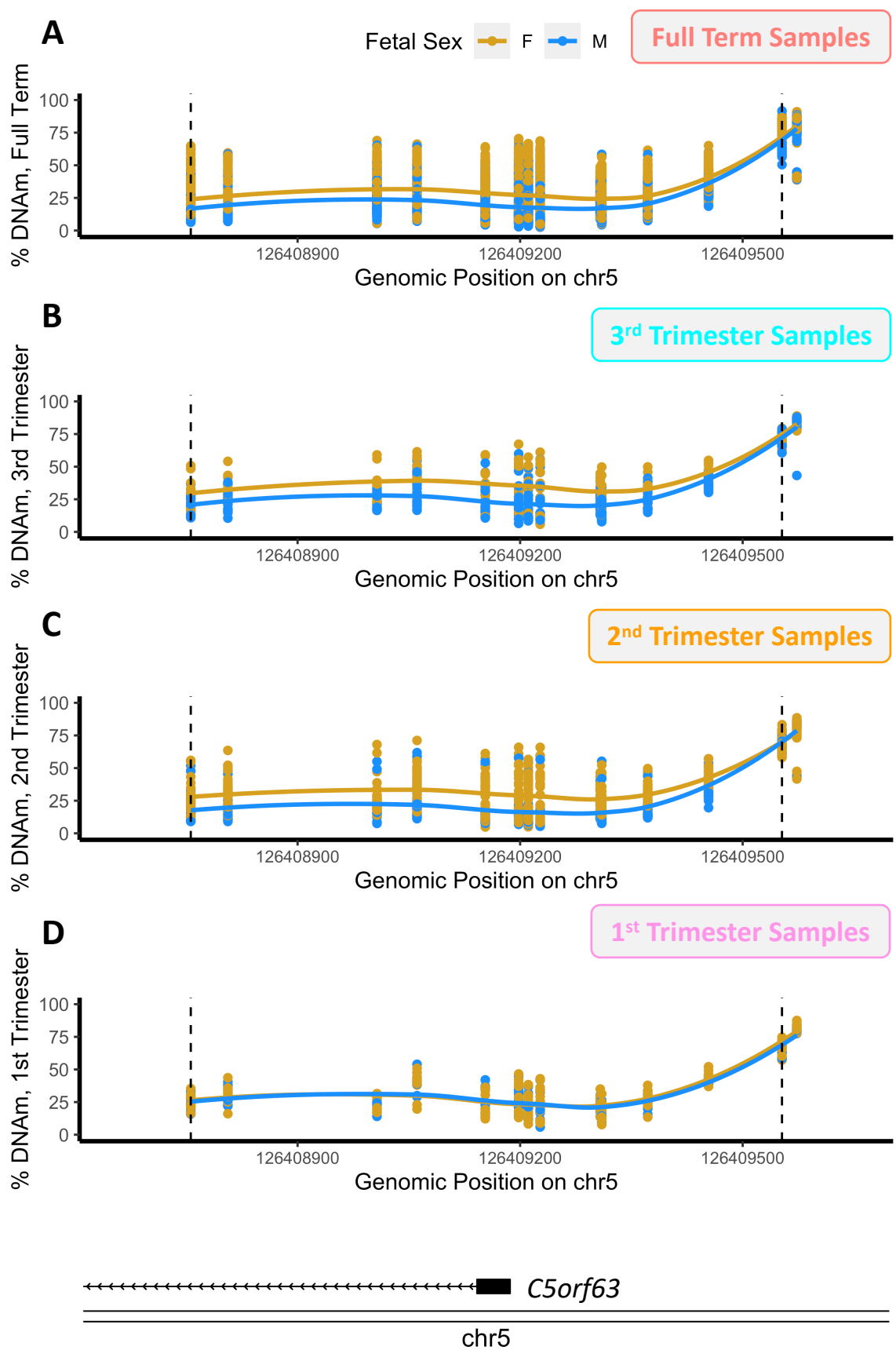
A**B****C**

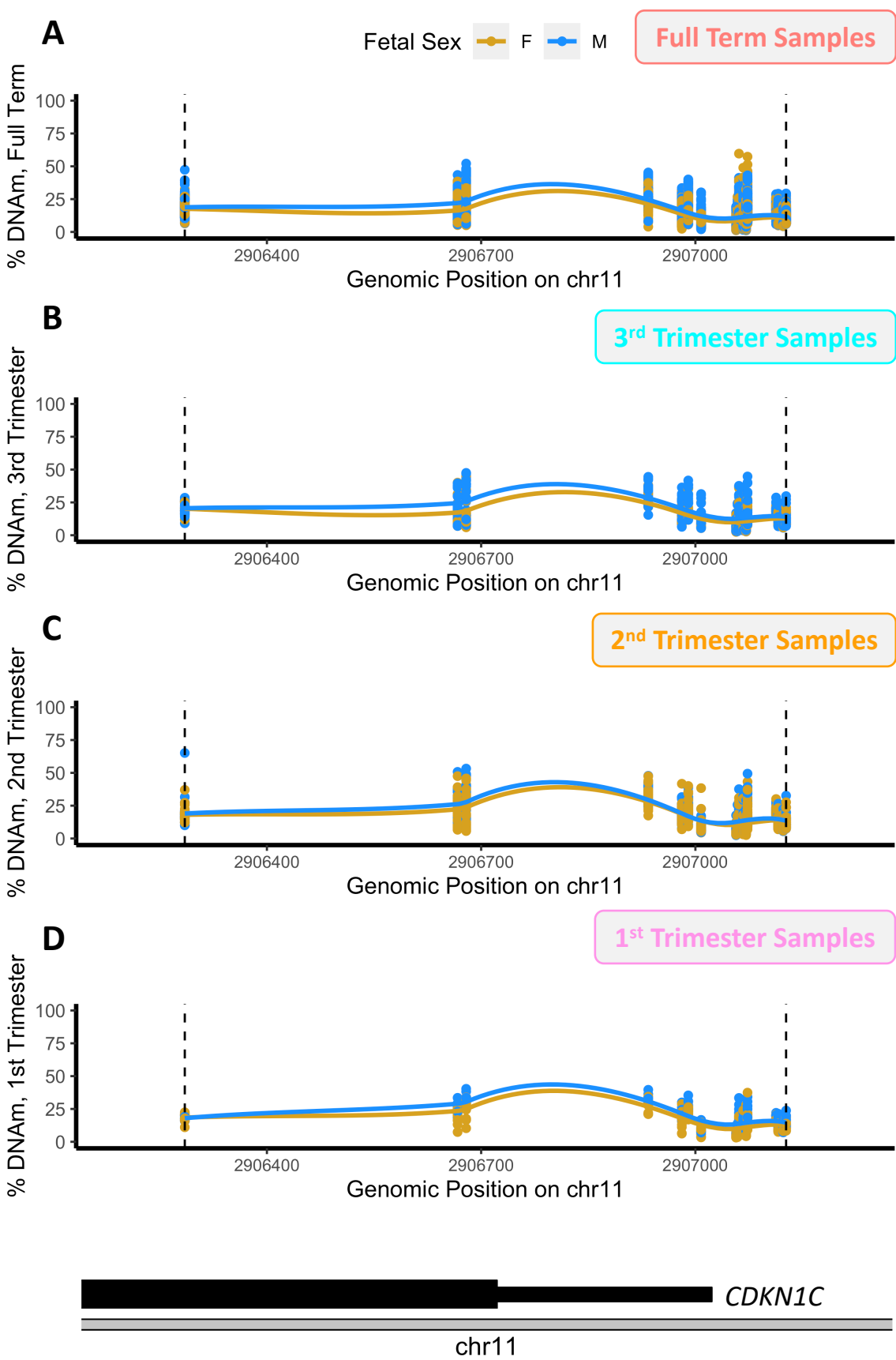


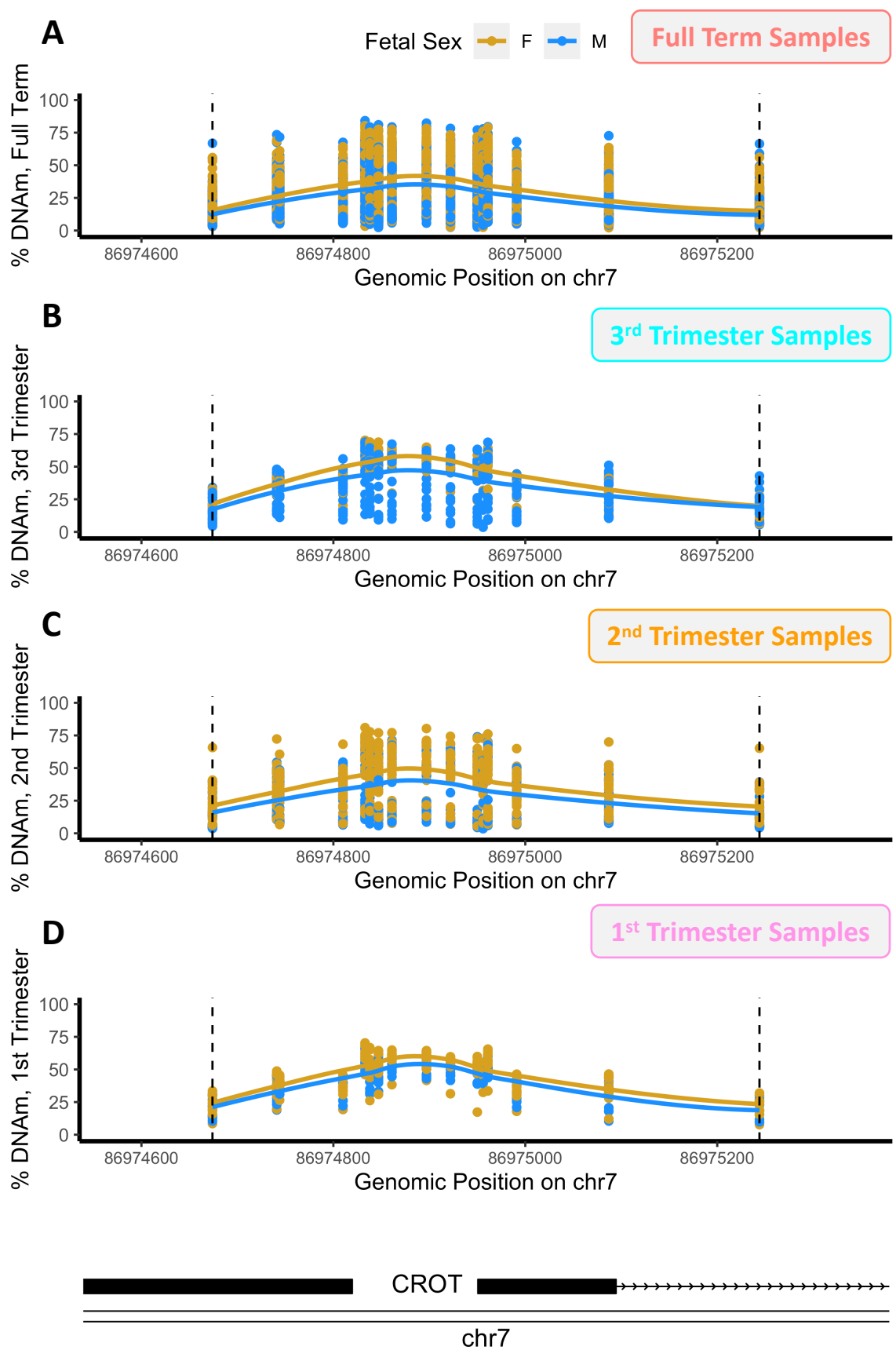


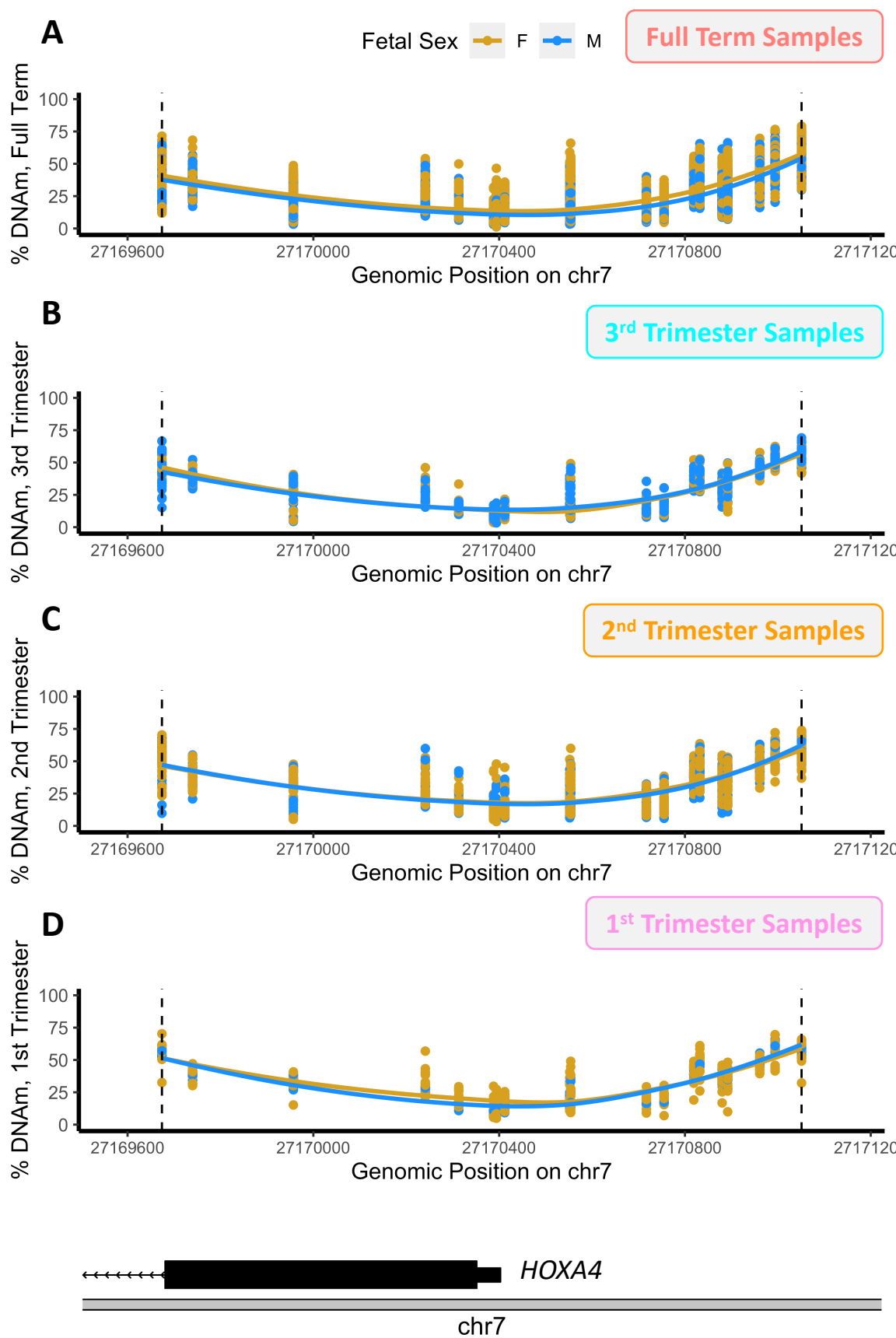
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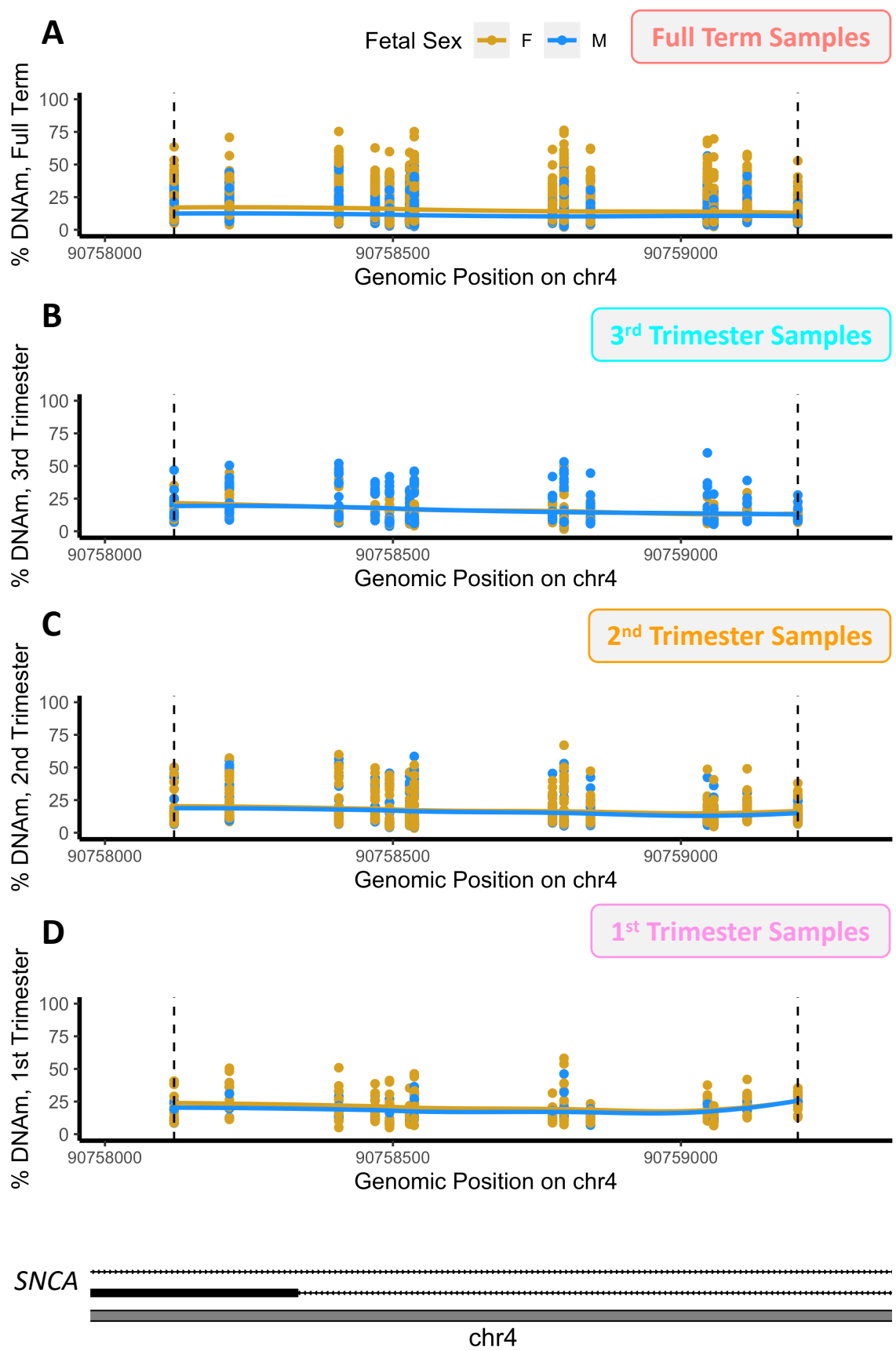
chr5

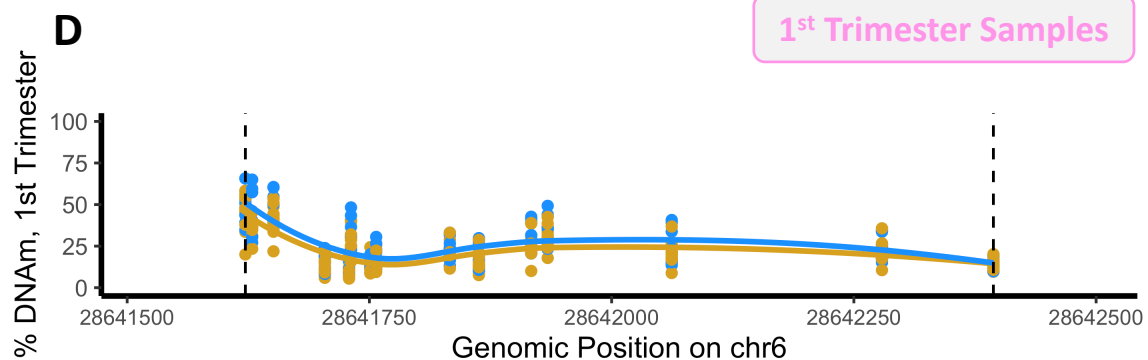
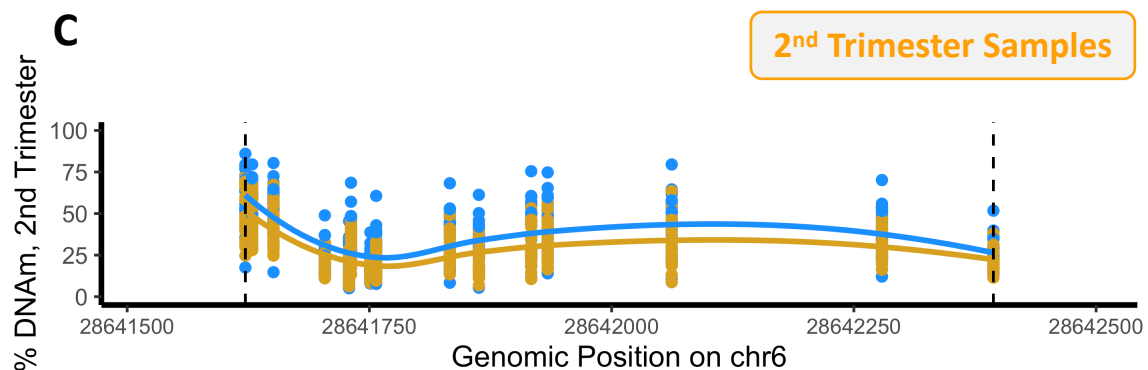
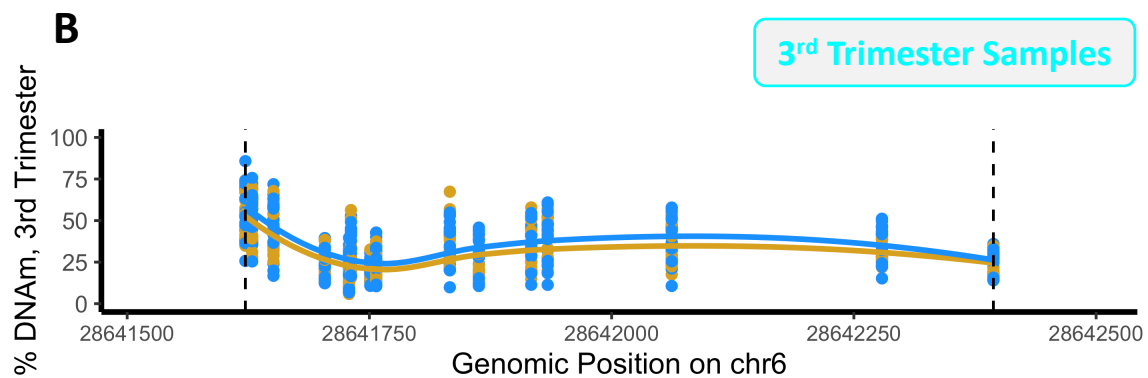
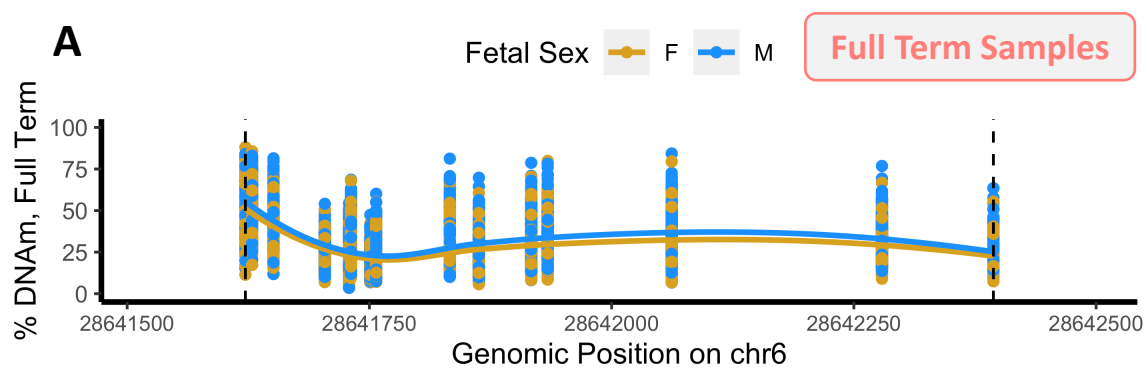












chr6

