

A Comprehensive Map of Epigenetic Inheritance in Mice

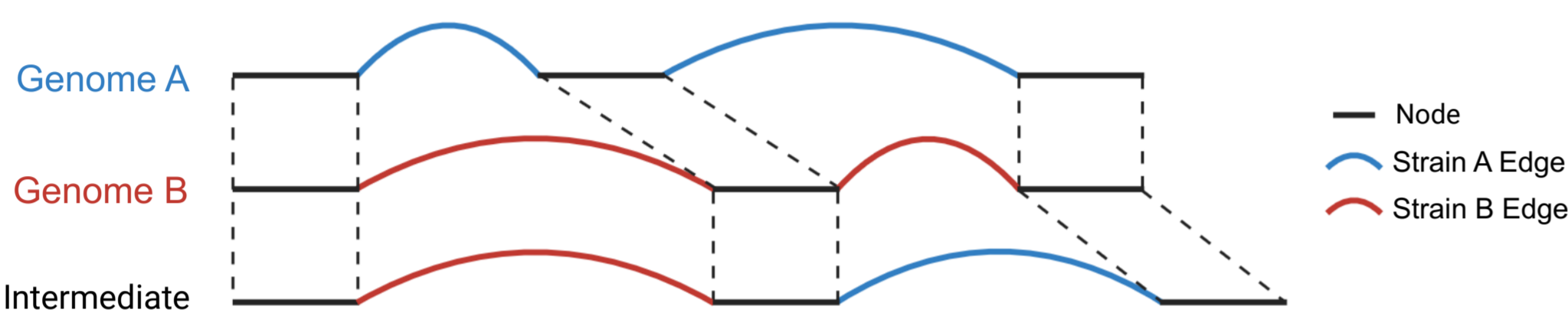
Adam Davidovich¹, Danila Cuomo², Sandeep Kambhampati¹, Hang Su³, Kasper D. Hansen⁴, David W. Threadgill², Andrew P. Feinberg¹

¹ Department of Biomedical Engineering, Johns Hopkins University School of Medicine, ² Department of Molecular and Cellular Medicine, Texas A&M University, ³ Department of Bioinformatics and Computational Biology, University of North Carolina, ⁴ Department of Biostatistics, Johns Hopkins University

DNA methylation has been shown to mediate the effects of both genotype and the environment on a variety of physiologically relevant phenotypes and is capable of being inherited in a multi-generational manner^[1]. Thus, the epigenome is an optimal candidate to help explain the vast number of heritable diseases and phenotypes which report a limited genetic contribution through genome-wide association studies (GWAS). An understanding of the relationship between the genome, epigenome, and transcriptome will help to determine the role played by epigenetics in the etiology of these diseases^[1]. Here, we use the Collaborative Cross (CC) mouse model and ONT sequencing to examine the relationship between genetic strain differences, DNA methylation, and gene expression. This analytical framework enables the identification of genomic loci with DNA methylation and gene expression controlled a wide range of complex inheritance patterns.

Methods

Creation of Intermediate Pseudo-Hybrid Genome



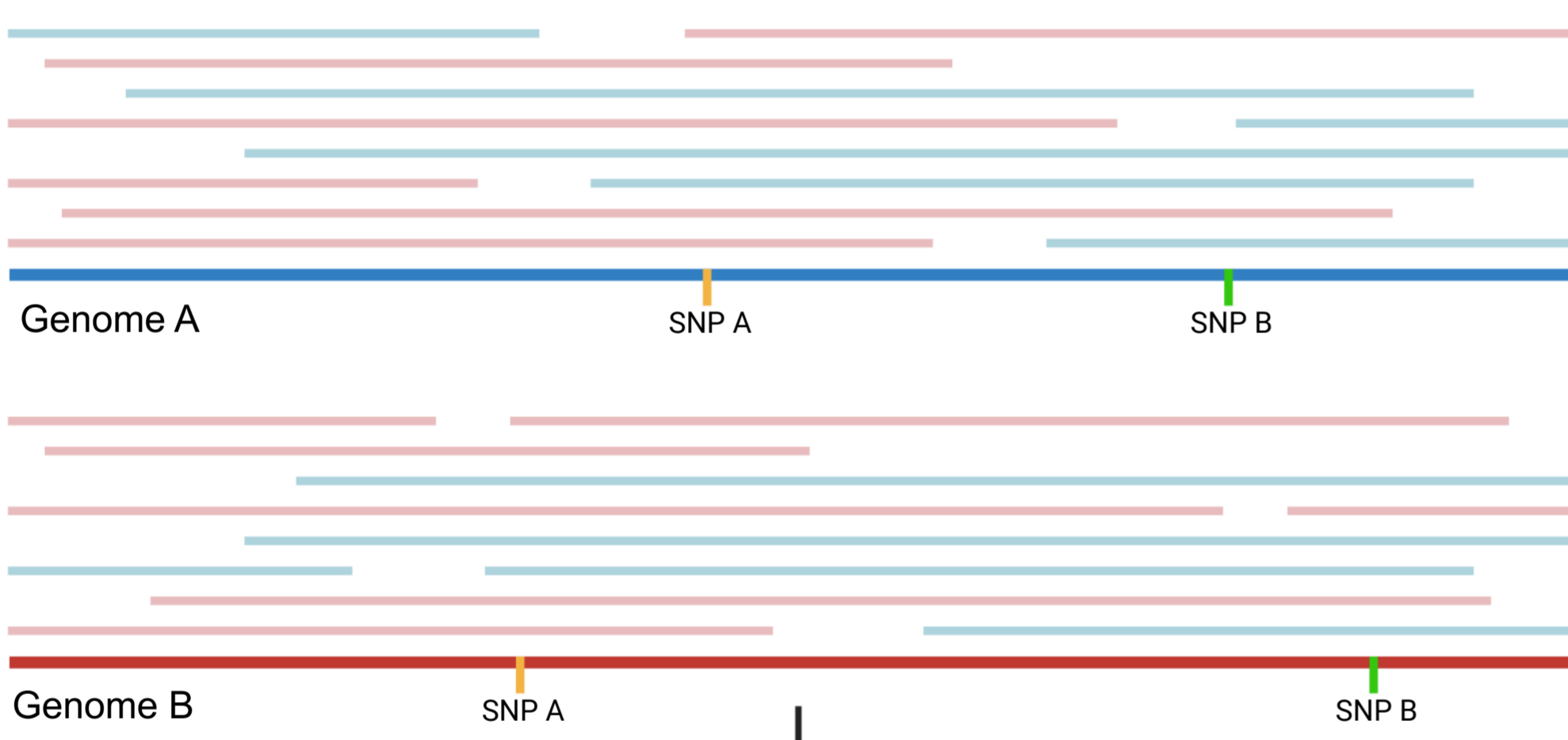
Identification of Heterozygous Genetic Variants from Genomes



Basecalling + Methylation Calling



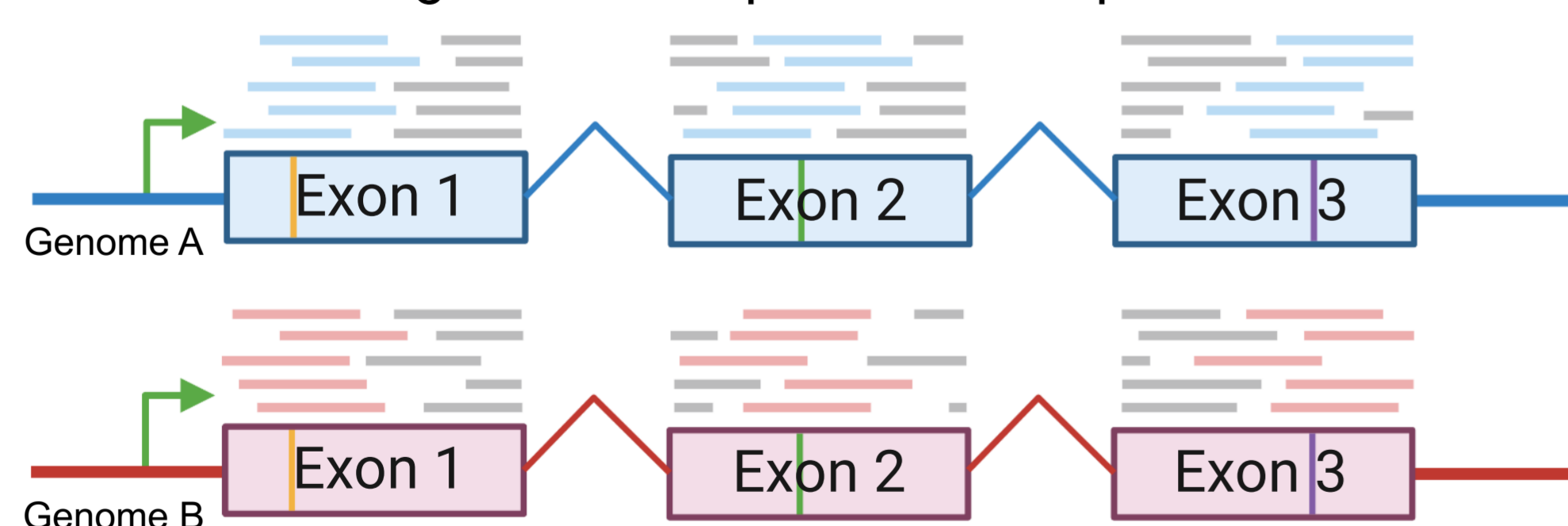
Alignment + Haplotyping



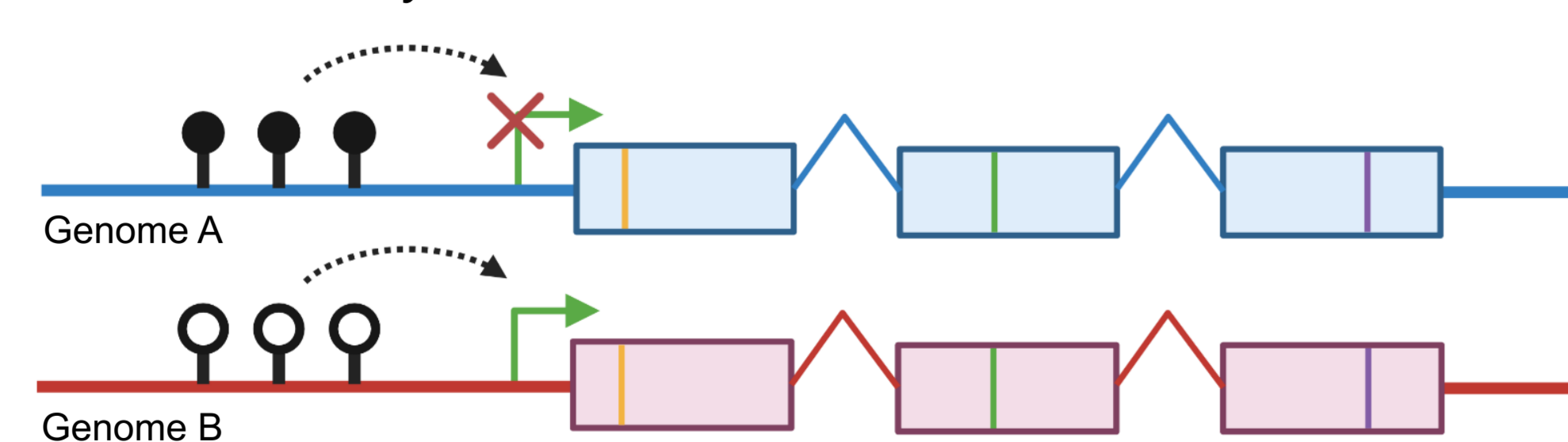
Consensus Haplotyping and Coordinate Conversion



Alignment to Diploid Transcriptome

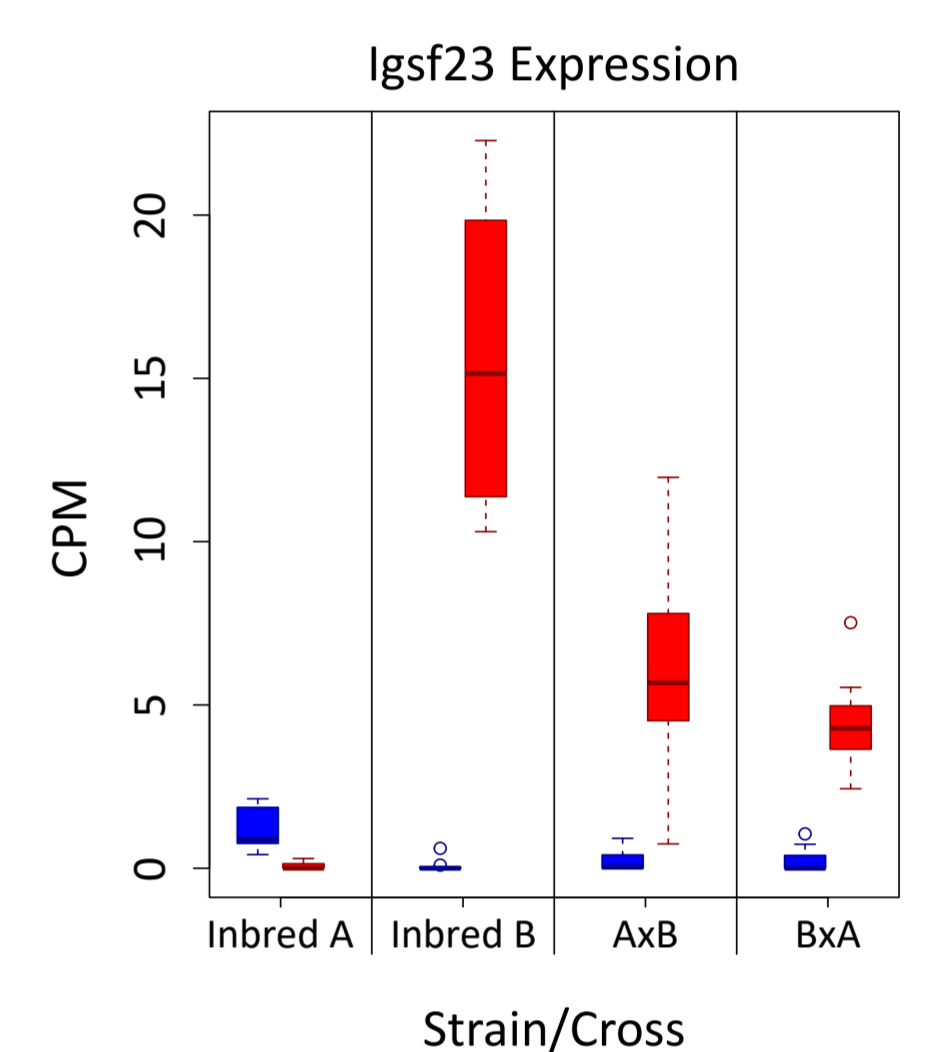
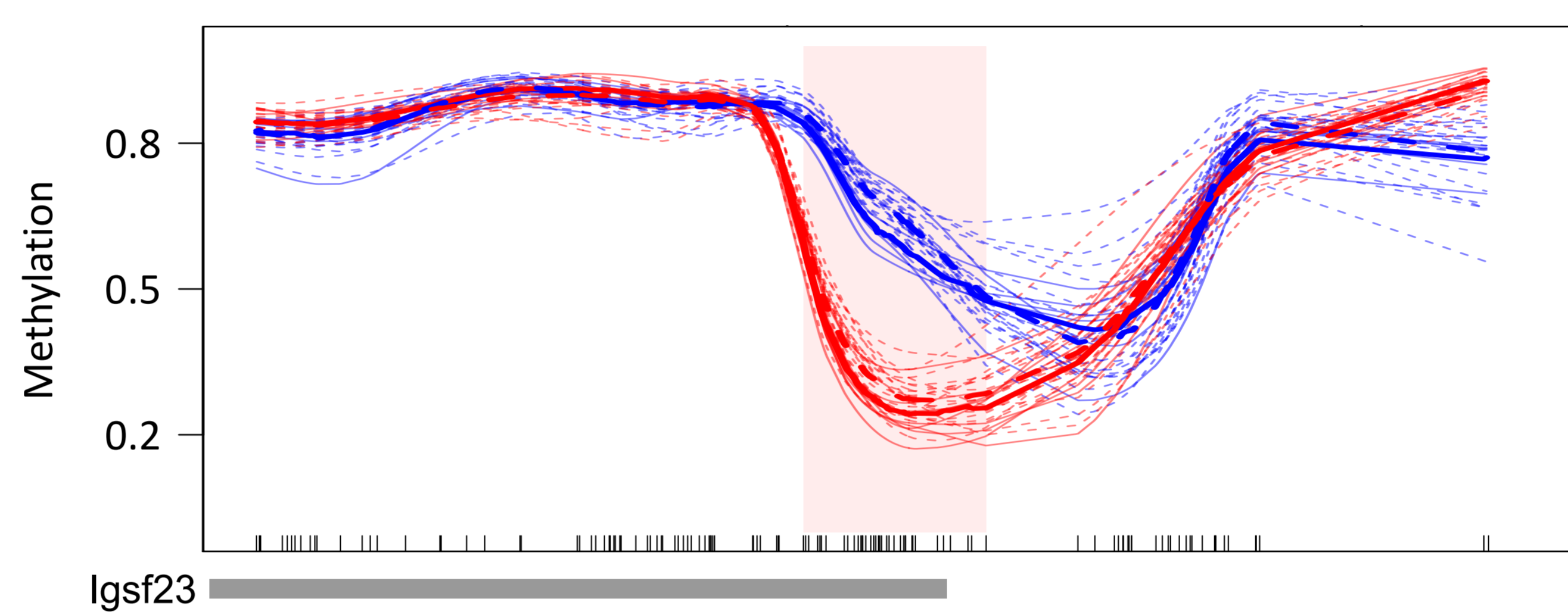


Gene-Level Analysis of Allelic Imbalance - Match ASM and ASE

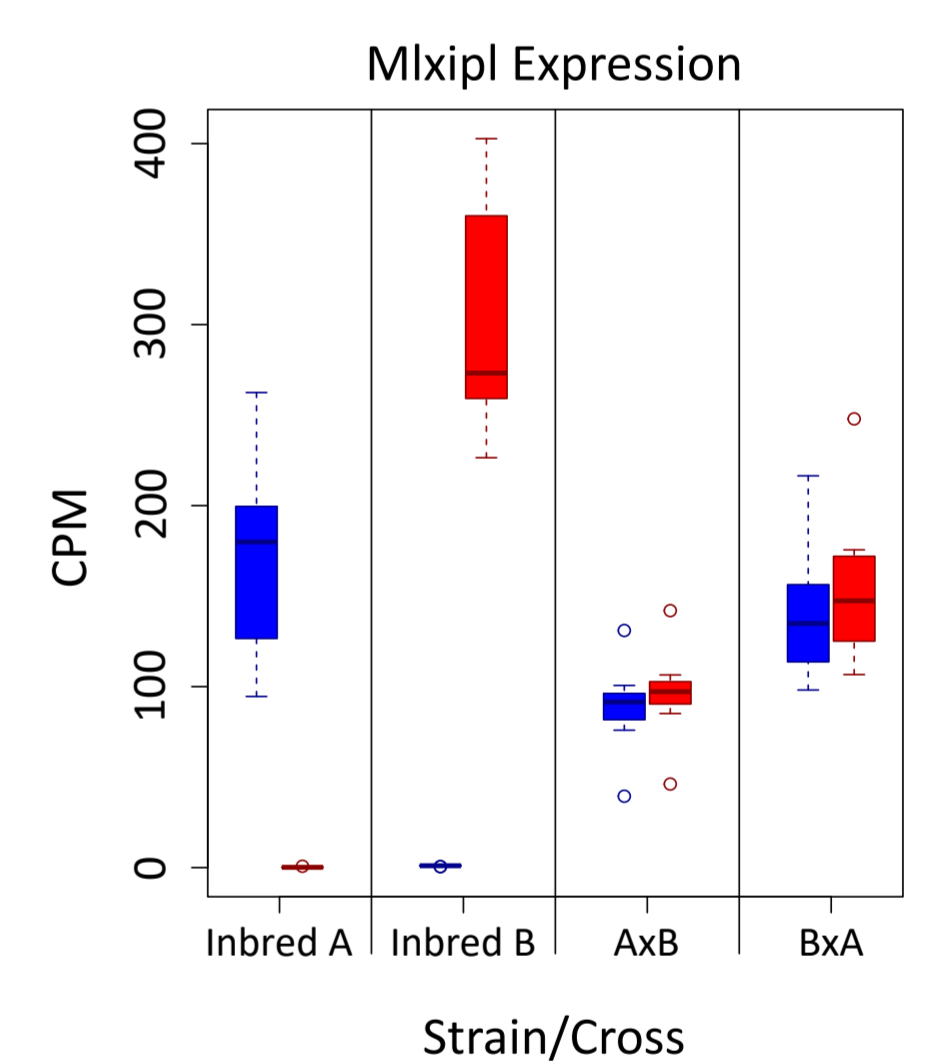
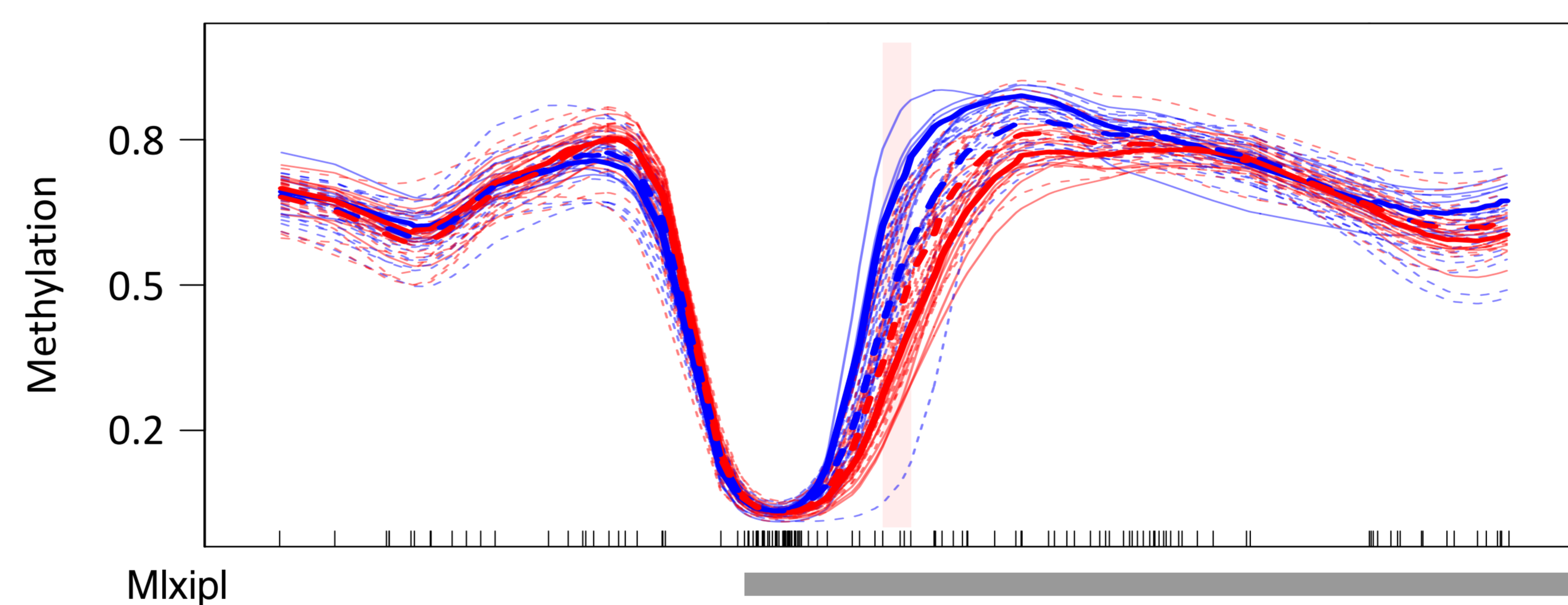


Complex Epigenetic Inheritance Patterns

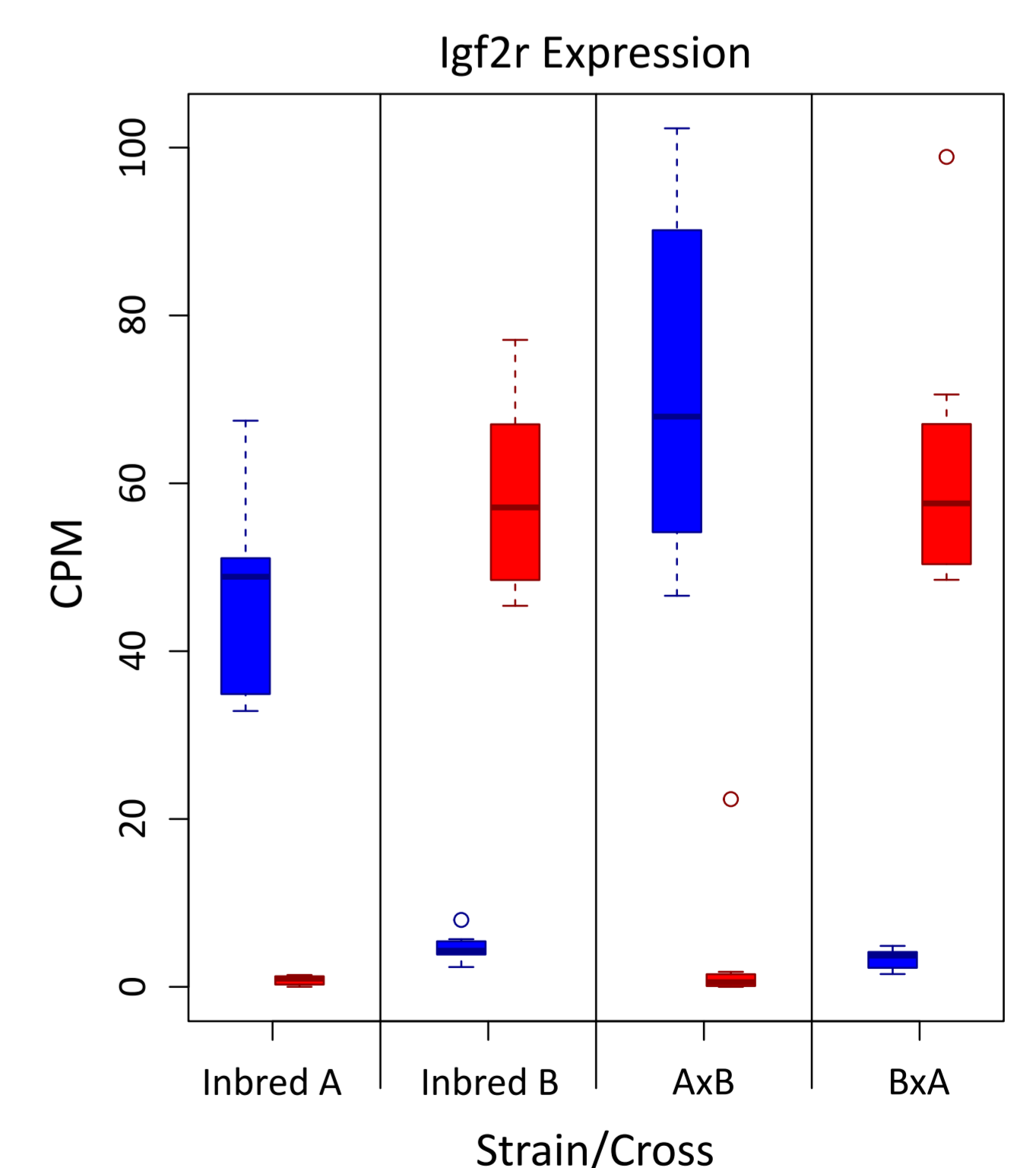
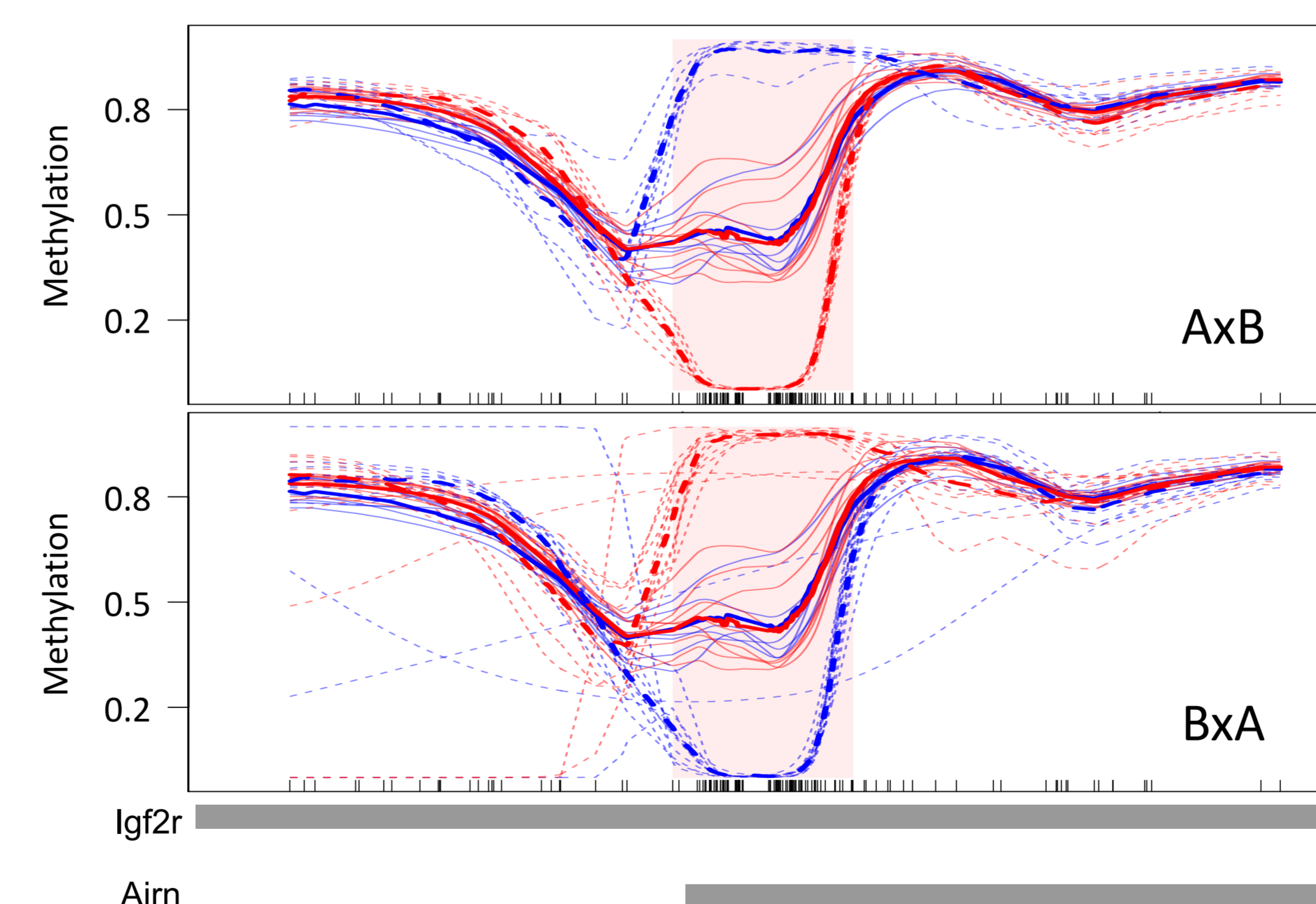
Cis DMR – Methylation stratifies by genotype – methylation is controlled by a cis-acting meQTL which will be present on and affect only the corresponding allele of the RIXs



Trans DMR – Methylation stratifies by genotype only in the inbred samples – methylation is controlled by a trans-acting meQTL which will affect both alleles; competing trans factors from each strain will establish intermediate methylation and expression levels in RIXs



Imprinting/Parent-of-Origin DMR – Methylation stratifies by parent of origin regardless of genotype or sex; stratification cannot be observed in inbred samples without haplotyping



— Inbred Strain A - - - RIX – Allele A
— Inbred Strain B - - - RIX – Allele B

Conclusion

This study highlights that ONT sequencing is a viable method for analyzing haplotype-resolved methylation data in the CC and enables a genome-wide assessment of parent-of-origin and strain-specific methylation effects. These results underscore the improved capabilities of our pipeline in identifying and mapping complex epigenetic inheritance patterns which cannot be studied at the genome-scale using current technologies.

References/ Acknowledgements

[1] Feinberg, A.P. *NEJM* (2018).
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BioRender.com