



# Sex Differences in the Intergenerational Link Between Maternal and Neonatal Whole Blood DNA Methylation: An Analysis in the Boston Birth Cohort

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## Introduction

- The intergenerational link in DNA methylation (DNAm) variation could contribute to the inheritance of disease susceptibility across generations.
- No study has investigated patterns of intergenerational link of DNAm at the genome-wide scale. It is also unknown whether there are sex differences in maternal-neonatal DNAm associations.

## Aims

- To examine mother-newborn correlations in overall DNAm patterns by newborn sex for all DNAm sites, as well as for autosomal and X-chromosomal DNAm sites separately.
- To identify individual DNAm sites (genes) with significant associations in methylation levels between mothers and their newborns, and test for differences in associations by newborn sex.

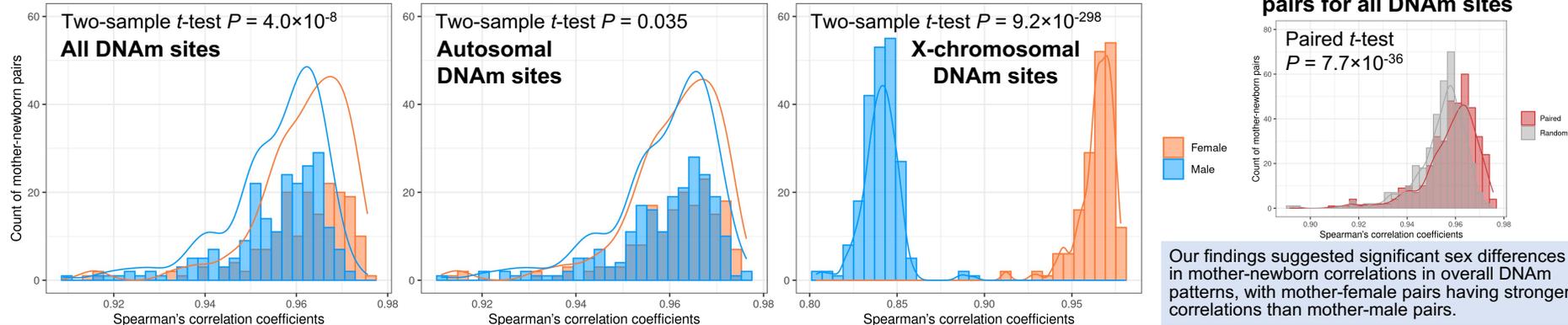
## Study population

- 396 mother-newborn pairs (54.5% male) from the Boston Birth Cohort, a predominantly urban, low-income minority birth cohort in Boston, MA.

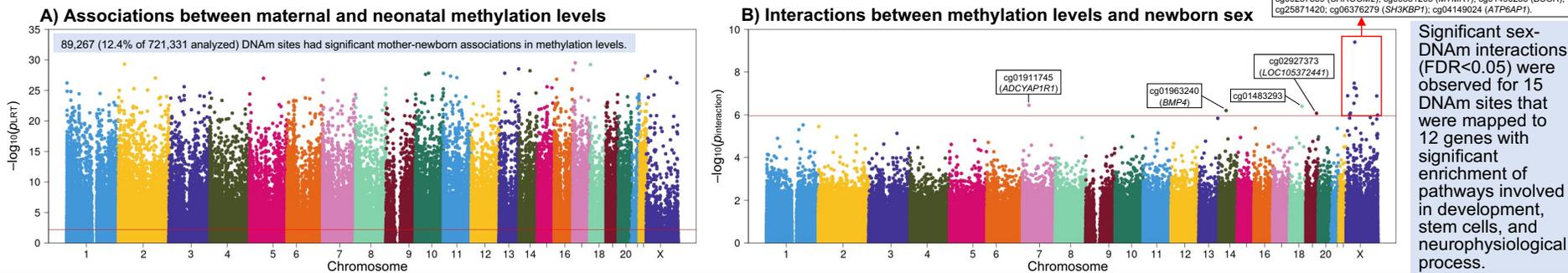
## DNA methylation profiling

- Genome-wide DNAm profiling was performed on maternal whole blood (obtained 24-72 hours after delivery) and neonatal cord blood samples using Illumina MethylationEPIC BeadChip.
- 721,331 DNAm sites on autosomes and the X chromosome (ChrX) were eligible for analysis after quality control steps, including removing probes mapped to multiple genomic regions.

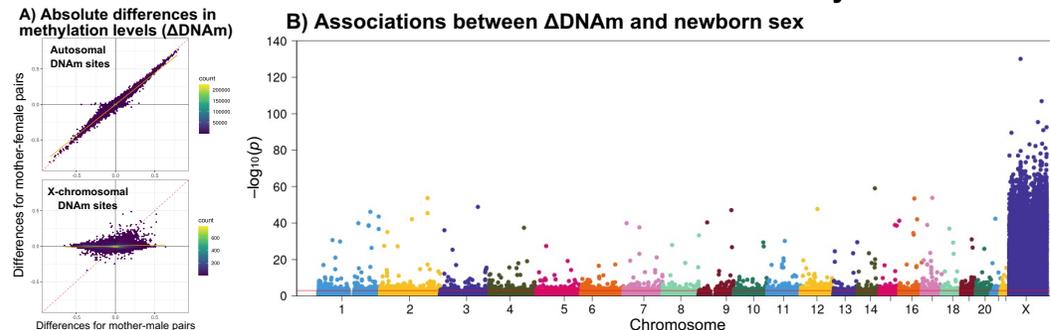
## Mother-newborn correlations in overall DNAm patterns



## Mother-newborn associations in methylation levels for individual DNAm sites



## Associations between mother-newborn differences in methylation levels and newborn sex



We observed that 18,769 DNAm sites (14,482 [77.2%] on ChrX) showed significant associations between mother-newborn differences in methylation levels and newborn sex; these DNAm sites were mapped to 3,510 genes with significant enrichment of pathways involved in neurodegenerative and psychological diseases, neurophysiological process, development, and sex-specific cancers.

## Conclusions

Mother-newborn associations in DNAm patterns significantly differ by newborn sex, particularly for ChrX, and there is more similarity of DNAm between mothers and their female newborns. Our findings might offer new insights into the developmental origins of many pediatric and adult diseases with remarkable sex differences in risk.

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