Title: Meta-analysis of ageing associated DNA methylation in X and Y chromosomes

Authors:
Joanna Ciantar, Sonja Rajić, Daria Kostiniuk, Lauren J. Gerber, Pashupati P. Mishra, Nina Mononen, Olli Raitakari, Terho Lehtimäki, Emma Raitoharju, Saara Marttila

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Abstract

Ageing has been associated with changes in DNA methylation. However, most genome-wide analyses have excluded X and Y chromosomes due to data normalization challenges caused by sex chromosome dosage differences. The few published studies focusing on sex chromosomes show limited overlap.

Here, we have identified ageing-associated DNA methylation changes in blood in X and Y chromosomes, separately for females and males, in six population cohorts (N=5717) consisting of individuals aged 18 to 88 years and performed a meta-analysis across the datasets. Furthermore, we validated the results in a longitudinal cohort spanning 25 years. We also sought to replicate our results in cerebral cortex samples (n=453).

Similar to autosomes, ageing-associated hypomethylation was more common than hypermethylation for loci in both X and Y chromosomes. The number and magnitude of the observed changes was also comparable to autosomes. Neuroligin genes were among the top hits and showed a consistent pattern of gene body hypomethylation and transcription start site hypermethylation. Neuroligins are expressed in the brain however, we did not identify ageing-associated DNA methylation changes in neuroligin genes in the cerebral cortex.

Neuroligins are an interesting example of ageing-associated DNA methylation changes which show a consistent pattern in a tissue where these genes are not primarily expressed and therefore warrant further study. Previously, autosomal neuroligins have also been reported to show ageing-associated DNA methylation changes. More broadly, our results highlight the need to implement methodologies and practices to include X and Y chromosomes when studying DNA methylation, for true genome-wide analyses.