

Title: Age-associated changes in non-CpG methylation in humans**Authors:**

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Abstract

Term 'DNA methylation' is typically understood to mean methylation of the CpG-site, i.e. methylation of cytosine adjacent to a guanine in the DNA strand. Majority of epigenetic studies have focused on CpG methylation, and it has a well-established role in gene expression regulation. However, non-CpG methylation, i.e. methylation of a cytosine adjacent to any other base in the DNA, is also widespread across the human genome, but this modification remains understudied.

Here, we have analysed non-CpG methylation in a population cohort (Young Finns Study, n=3390, aged 18 to 92 years). Methylation levels were measured from whole blood DNA with the Illumina Infinium EPIC array. Non-CpG methylation levels were low as compared to CpG methylation, with a median methylation level of only 4%. We analysed association to age, and out of the 2832 non-CpG sites present in the array 671 (24%) were associated with age ($p_{FDR} < 0.05$); all but one of these sites were hypomethylated. The age-associated probes were mainly located in regions 1500 nucleotides upstream of transcription start site and in the 5'UTR, whereas they were mainly absent from gene bodies.

As we identified hypomethylation at methylation sites that display low levels of methylation to begin with, the observed effect was very modest, suggesting also modest functional effects. Rather, the observed pattern most likely is linked to the overall remodelling of the epigenetic landscape with age. Our next step is to replicate our findings in independent cohorts and to characterise the age-associated non-CpG methylation sites further.