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Examination of folate and dietary factors influencing the methylome in healthy adult females

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Epigenetics refers to heritable changes in a gene's activity that do not involve changes to the DNA sequence[(1)]. The methylome is used to describe modifications within a genome as a result of DNA methylation, one of the earliest studied epigenetic markers[(2)]. Alterations in DNA methylation patterns influence gene expression levels and have been associated with diseases like cancer and neurological disorders[(1)]. Despite major advances in interpreting the methylome, understanding its interaction with diet and lifestyle is far from complete. Methylation of DNA occurs via the methyl donor S-adenosylmethionine (SAM). Maintenance of tissue SAM concentrations is heavily dependent on B vitamin function, especially folate and vitamins B-2, B6 and B-12[(2)]. We hypothesised that B vitamin intakes would influence methylation status. The aim of this study was first to investigate the effect of extremes of folate status on global and gene-specific methylation patterns and second to assess interactions with status of other micronutrients, specifically vitamins B-2 and B-12.

Sixty-three age and BMI-matched females were selected from the Irish National Adult Nutrition Survey (NANS) cohort (www.iuna.net). A 4-day semi-weighed food diary and blood biomarkers were used to place participants into the High Folate (n = 34) or Low Folate group (n = 29) based on dietary folate intake, serum folate, red cell folate (RCF), serum B12 and plasma homocysteine. Blood methylation profiles were examined using the HumanMethylation27 DNA Analysis BeadChip by *Ilumina*. Global methylation patterns were determined and compared between the two groups using *T*-tests. The impact of B vitamin status, adjusting for other lifestyle factors', were investigated using linear regression and predictive modelling. Genes with significantly different methylated sites (at $P < 0{\cdot}001$) between the folate groups were clustered using DAVID Gene Functional Clustering tool.

Extremes of folate intake had no significant effect on global methylation. As a total group no associations were found between global methylation and the measured dietary factors however in the low folate group alone Vitamins B-12 and B-2 were significantly associated with global methylation ($P = 0{\cdot}016$, $P = 0{\cdot}032$ respectively). Some differences were found in relation to gene-specific methylation. Methylation patterns at 259 CpG sites were significantly different between the high and low folate groups ($P > 0{\cdot}001$). 241 CpG sites had increased methylation levels in the high folate group and 9 gene functional clusters were created. These clusters were made up of protein-coding genes specifically in relation to kinases, cell development and cell functioning.

In conclusion, no change in overall global methylation was seen in relation to folate intake. An association between vitamin B-12 and B-2 intakes with the methylome were identified and findings suggest that the impact of other nutrients on the methylome become more important with low folate status. Certain functional genes may be sensitive to folate-mediated methylation, particularly relating to cell development and functioning.

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