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The impact of the MTHFR 677C>T polymorphism on RUNX1 DNA methylation patterns

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Folate/riboflavin status in combination with the MTHFR 677C>T genotype have previously been identified as important factors for consideration in health and disease[1]. The molecular mechanism of this genotype–nutrient interaction is far from clear, but several theories have been proposed; among these is an impact on DNA methylation. The folate metabolic pathway provides 1-carbons for both DNA synthesis and methylation reactions. Thus, the link between folate status, folate enzyme polymorphisms and a possible impact on DNA methylation has a strong biological basis.

We identified RUNX1 as a responder to changes in folate/riboflavin status and by inhibition of the methylation cycle in cell culture models by examining gene expression changes using Affymextrix HG U133 plus 2.0 GeneChips. We reasoned that DNA methylation changes in the promoter region may be mediating these gene expression changes. RUNX1 is a transcription factor that has a number of roles but is primarily involved in the development of all haematopoietic cell types[2].

In the present study, we assessed whether DNA methylation in the proximal promoter of RUNX1 correlated with MTHFR 677C>T genotype. DNA methylation within a CpG island of the proximal promoter of RUNX1 was assessed by methylation-sensitive high-resolution melting (MS-HRM) incorporating primer and assay design recommendations as described by Wojdacz *et al.*[3]. DNA methylation was assessed in a panel of DNA samples of known MTHFR 677C>T genotype from the Coriell lymphoblast collection.

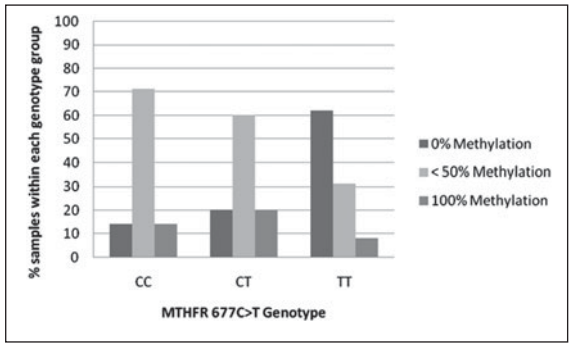

Figure. RUNX1 DNA methylation patterns as assessed by MS-HRM in DNA samples of known MTHFR 677C>T genotype (CC: *n* 7; CT: *n* 5; TT: *n*13). Each sample was run in duplicate. The MTHFR 677TT genotype group showed an enrichment of samples with 0% DNA methylation compared to CC or CT groups.

Comparison of the DNA methylation profiles of each genotype group shows that the CC and CT groups have a broadly similar pattern. The TT group, however, shows a dramatic enrichment of samples with 0% DNA methylation of their RUNX1 proximal promoter. The methylation profile of the TT group was compared to a combined CC/CT profile by Mann–Whitney test using SPSS yielding a *P*-value of 0.06, i.e. not significant. In conclusion, TT individuals may tend to exhibit 0% DNA methylation of their proximal RUNX1 promoter compared to CC or CT individuals particularly in the context of nutritional status. This is likely to have an influence during development when the regulation of the switch between the proximal and distal promoter is crucial[2]. However, this needs to be assessed in a larger sample set and in DNA isolated from different tissues.

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2. Cohen MM Jr (2009) *Am J Med Genet* A **149**, 2629–2646.
3. Wojdacz TK, Dobrovic A & Hansen LL (2008) *Nat Protocols* **3**, 1903–1908.