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Traditionally, DNA methylation has been thought of as being involved in gene silencing, but work in recent years has shown a more complex picture, and the relationship between DNA methylation and gene expression remains unclear. Furthermore, as DNA methylation can be influenced by developmental and environmental factors, its relationship to genetic variation is also uncertain. A recent study of samples from a human cohort has sought to dissect these issues and highlights the context-dependent nature of DNA methylation and its functions.

Gutierrez-Arcelus *et al.* analysed DNA methylation, single-nucleotide polymorphism (SNP) genetic variation and gene expression across the genomes of fibroblasts, lymphoblastoid cells and T cells derived from umbilical cord samples from ~200 healthy newborns. From these data, they were able to identify loci that affect gene expression (namely, expression quantitative trait loci (eQTLs)), loci that affect DNA methylation (namely, methylation QTLs (mQTLs)) and methylated sites that are associated with gene expression (namely, eQTMs).

First the authors considered how DNA methylation differences among the three cell types relate to differences among individuals. They found that methylation sites involved in eQTMs and mQTLs — that is, sites associated with variation among the individuals — tend to differ more among cell types, which suggests that sites subject to developmental changes in DNA methylation also contribute to inter-individual differences in methylation. However, the degree to which inter-individual differences in methylation are under genetic control seems to be intricately linked to genomic location. For example, methylation in the context of promoters that lack CpG islands seems to be more strongly influenced by genetic variation than does methylation at CpG island promoters.

A crucial issue for interpreting differences in DNA methylation is understanding whether this mark has a passive or an active role in gene regulation. To address this question, the authors considered three possible models: the 'independent' model, in which a SNP separately influences gene expression and DNA methylation; the 'SNP–methylation–expression' model, in which a SNP affects methylation, and this methylation influences expression; and the 'SNP–expression–methylation' model, in which the SNP affects expression, and this expression consequently alters methylation. They found that all three models occur in different contexts. Notably, the SNP–methylation–expression model — the only one in which DNA methylation has an active role in regulation — is frequent in T cells but not in fibroblasts or lymphoblastoid cells, in which the independent model predominates.

To understand further how the independent model might operate, the authors looked at the relationship between DNA methylation and transcription factor binding. Their data support a model in which genetic variation can influence transcription factor binding, and this binding can independently affect gene expression and DNA methylation levels.

These results caution against any simplistic interpretation of the causes and consequences of variation in DNA methylation, and similar complexities may exist for other epigenetic marks, such as some histone modifications.

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ORIGINAL RESEARCH PAPER Gutierrez-Arcelus, M. *et al.* Passive and active DNA methylation and the interplay with genetic variation in gene regulation. *eLife* **2**, e00523 (2013)
FURTHER READING Jones, P. A. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nature Rev. Genet.* **13**, 484–492 (2012)