


**GENE EXPRESSION**

## Layers of gene regulation

A new study investigates genetic and epigenetic influences on genome regulation and alternative splicing, and highlights the tissue specificity of some of these interactions.

In a previous study, the researchers examined the relationship between genetic variation, DNA methylation and gene expression using samples from the GenCord cohort that were derived from umbilical cords of 204 newborn children. They genotyped 2.5 million single-nucleotide polymorphisms (SNPs), assayed the methylation levels of 482,421 CpG sites and sequenced the transcriptomes from three cell types — fibroblasts, lymphoblastoid cell lines (LCLs) and T cells. Extending this work, the team now further characterize the effects of genetic and epigenetic variation on the tissue specificity of gene expression and alternative splicing.

Gutierrez-Arcelus *et al.* find that genetic variation affecting gene

expression and DNA methylation levels often overlap functional elements. Across cell types, expression quantitative trait loci (eQTLs) are enriched in DNase I-hypersensitive sites, whereas methylation QTLs (mQTLs) are enriched in enhancers and insulators. Their statistical analyses show that, generally, genetic variation has a more consistent effect on gene expression across cell types, although the strength of the effect can be variable. However, the effects of epigenetic variation on gene expression are more tissue-specific. Methylation sites that are associated with expression levels are found predominantly in enhancers, gene bodies and CpG shores, and the correlation with gene expression can be either positive or negative.

Alternative splicing levels were measured to see whether there was a tissue-specific correlation with genetic variation and DNA

methylation. Spearman's rank correlation between methylation levels (within 50 kb on either side of the transcription start site) and alternative splicing levels show that, for many of the genes tested, there is a significant association. Of note, many of the associations between DNA methylation and alternative splicing are cell type-specific, illustrating another layer of cellular variability.

A complex relationship between DNA methylation and gene expression is beginning to emerge. This study further defines the roles of genomic and epigenomic variation in determining cellular phenotypes, and the mechanisms by which these effects might occur. It also highlights that regulatory principles and mechanisms identified in one tissue type cannot necessarily be extrapolated to other tissue types.

Bryony Jones

**ORIGINAL RESEARCH PAPER**

Gutierrez-Arcelus, M. *et al.* Tissue-specific effects of genetic and epigenetic variation on gene regulation and splicing. *PLoS Genet.* **11**, e1004958 (2015)



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