P. Morgan/NPG

GENE REGULATION

From genetic variation to phenotype via chromatin

There is known to be some correlation among genetic variation, chromatin modifications, transcription factor binding, gene expression and phenotypes. However, the jury is still out on the strength of the links between these different organismal features and whether alterations in one directly cause alterations in the other. Four studies have now taken advantage of recently developed genome-wide approaches and resources in both humans and mice to establish that genetic variation strongly determines sites of transcription factor binding. This binding, in turn, results in altered histone modifications and enhancer choice, which lead to changes in both gene expression and the resultant phenotypes.

McVicker *et al.* and Kilpinen *et al.* took a similar approach, which was to carry out chromatin immunoprecipitation followed by sequencing (ChIP-seq) to survey histone modifications,

transcription factor binding and actively transcribed sites as defined by the locations of RNA polymerase II. Kilpinen *et al.* analysed these features in lymphoblastoid cell lines (LCLs) from parent–offspring trios and from eight unrelated individuals in the 1,000 Genomes Project, whereas McVicker *et al.* surveyed LCLs from ten unrelated Yoruba individuals. Both studies found allelic specificity of histone modifications, which, importantly, was coordinated with transcription factor binding. This finding indicates that sequence-specific transcription factors may specify histone modifications, and that there is thus a sequence-specific component to the deposition of histone modifications. This allelic specificity leads, in turn, to changes in both enhancer choice and gene expression between different haplotypes, even in distal enhancers.

The approach of Kasowski *et al.* was to map histone modifications by ChIP-seq and gene expression by RNA sequencing in 19 individuals from the 1,000 Genomes Project. In addition, the locations of two general transcription factors were mapped. By dividing the genome into regions with different combinations of chromatin modifications, they found that there are extensive differences in enhancer states between individuals, as well as in transcription factor-binding sites that are associated with different chromatin states. However, they found that, to alter gene expression, multiple enhancers that are linked to a gene must have alterations in their histone modification states.

Heinz *et al.* also used natural genetic variation as their ‘*in vivo* mutagenesis screen’—they looked at differences in transcription factor binding and in histone modifications between the C57BL/6J and BALB/cJ strains of mice. They investigated the binding of the proposed lineage-defining transcription factors (LDTFs) PU.1 and CCAAT/enhancer-binding protein- α , as well as the signalling-responsive transcription factor NF- κ B. They found that the binding of the proposed LDTFs is dependent on genetic variation, as are histone modifications, which suggests that these LDTFs determine histone modification patterns. Furthermore, the LDTFs seem to recruit each other, and they also seem to determine the binding of NF- κ B in response to signals.

The overarching theme of these papers is that genetic variation may determine sites of transcription factor binding, which, in turn, specify histone modifications and enhancer choice; however, some combinational alterations are required for gene expression changes.

Hannah Stower

ORIGINAL RESEARCH PAPERS Heinz, S. *et al.* Effect of natural genetic variation on enhancer selection and function. *Nature* <http://dx.doi.org/10.1038/nature12615> (2013) | Kasowski, M. *et al.* Extensive variation in chromatin states across humans. *Science* <http://dx.doi.org/10.1126/science.1242510> (2013) | Kilpinen, H. *et al.* Coordinated effects of sequence variation on DNA binding, chromatin structure, and transcription. *Science* <http://dx.doi.org/10.1126/science.1242463> (2013) | McVicker, G. *et al.* Identification of genetic variants that affect histone modifications in human cells. *Science* <http://dx.doi.org/10.1126/science.1242429> (2013)