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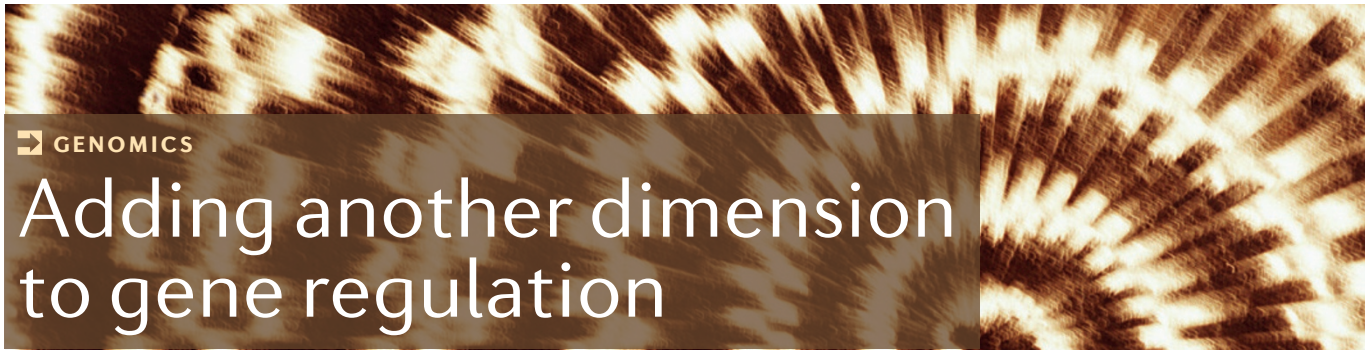

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GENOMICS

Adding another dimension to gene regulation

> different elements form intricate networks to modulate gene expression

Previous studies have shown extensive variation in chromatin states across humans, specifically in gene regulatory elements. Two studies published in *Cell* now provide mechanistic insights into the role of genome architecture in regulatory variation in humans and further elucidate how regulatory sequences interact to affect gene expression.

Both teams used chromatin immunoprecipitation followed by sequencing (ChIP–seq) to generate maps of three histone modifications that are known to be associated with promoters and/or enhancers (histone 3 lysine 4 monomethylation (H3K4me1), H3K4me3 and histone 3 lysine 27 acetylation (H3K27ac)) in lymphoblastoid cell lines (LCLs) from sequenced individuals. The teams then used quantitative trait locus (QTL) mapping to determine genetic variants associated with changes in the three histone marks (histone QTLs (hQTLs)), chromatin accessibility and RNA expression levels (expression QTLs (eQTLs)).

The cohort in the study by Grubert *et al.* consisted of 75 sequenced individuals. Of 933 local (that is, <2 kb from the QTL-associated single-nucleotide polymorphism (SNP)) eQTLs detected, two-thirds were found to also be local hQTLs, which means that the variation in histone marks is associated with variation in the expression levels of nearby genes. To determine whether the effect of genetic variants on local variation in chromatin state also propagates to distal (that is, >50 kb from the QTL-associated SNP) QTLs that are physically connected, the investigators integrated the chromatin profiling data with LCL-specific chromatin contact maps generated by Hi-C and chromatin interaction analysis by paired-end tag sequencing (ChIA–PET). A total of 15% of proximal hQTLs were associated with changes in chromatin states at distal genomic regions with which they interact physically. Distal chromatin QTLs were found to be enriched within topologically associated domains, which are known for their high frequency of physical interactions, and local–distal QTL pairs involved predominantly associations between pairs of enhancers. The authors posit that specific genetic variants within regulatory elements "may concordantly affect local and distal histone modifications through interacting networks of elements".

Waszak *et al.* profiled histone marks and gene expression in LCLs from 47 sequenced individuals from a different cohort. In addition, they also mapped enrichment patterns of the transcription factor PU.1 and RNA polymerase II. QTLs were mapped for all studied molecular phenotypes independently in a 500 kb window around the centre of a candidate regulatory element (or transcription start site). The findings reveal extensive coordination in chromatin variation at and between *cis*-regulatory elements within small (<1 Mb) genomic compartments, which the authors term variable chromatin modules (VCMs). Chromatin activity was also shown to be influenced by distally acting genetic variants. Both teams suggest that disruption of transcription factor–DNA interactions underlies the changes in chromatin activity that influence gene expression.

Jointly, these studies highlight the versatility and complexity of gene regulation, whereby different elements form intricate networks to modulate gene expression, for example, through changes in chromatin activity. Importantly, it is now evident that a single genetic variant can affect multiple, spatially separate gene regulatory elements at the same time.

The relevance to medical genomics is evident, as the findings indicate that if one element within a network is disrupted, the whole system is perturbed, which could lead to disease. By using the approaches developed by both teams, it might be possible to link genetic variants — detected, for example, in genome-wide association studies — to their regulatory network to ultimately identify the associated gene.

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ORIGINAL RESEARCH PAPERS Grubert, F. *et al.* Genetic control of chromatin states in humans involves local and distal chromosomal interactions. *Cell* **162**, 1051–1065 (2015) | Waszak, S. M. *et al.* Population variation and genetic control of modular chromatin architecture in humans. *Cell* **162**, 1039–1050 (2015)