of joint populations or of populations stratified by self-identified race or ethnicity, with African American populations having weaker effect sizes than Hispanic/Latino populations. These data emphasize that effect sizes and risk prediction scores derived from one population cannot be assumed to apply to different populations.

Next, the authors showed that data from genetically diverse populations can help fine-map associations, reducing the number of candidate causative variants. A meta-analysis that combined PAGE with GIANT data (from more than 250,000 individuals of European ancestry) reduced the average 95% credible set size from 11.94 SNPs to 9.68 for 390 variants associated with height in GIANT; by contrast, addition of data from 50,000 randomly sampled white British participants from the UK Biobank (UKB50k) to GIANT had no significant effect.

Finally, the authors demonstrated the importance of ancestry-specific findings for medically relevant variants. For example, genetic variants in haemoglobin are known to affect the results of glycated haemoglobin (HbA_{1c}) assays, which are used to diagnose and monitor type 2 diabetes mellitus. The PAGE study identified an association between a missense variant in the *HBB* gene (which encodes the haemoglobin β-chain) and HbA_{1c} levels in the Hispanic/Latino population, an association that had been previously reported for African Americans. Given the shared African ancestry of African Americans and some Hispanic/Latinos, this result suggests that ancestry-specific findings from one group may have relevance for other groups that share components of that genetic ancestry.

Taken together, the findings of this study powerfully illustrate the need for a more inclusive approach to GWAS if genetic discovery and precision medicine are to benefit everyone, regardless of genetic ancestry.

Dorothy Clyde

ORIGINAL ARTICLE Wojcik, G. L. et al. Genetic analyses of diverse populations improves discovery for complex traits. *Nature* **570**, 514–518 (2019)
FURTHER READING Gurdasani, D. et al. Genomics of disease risk in globally diverse populations. *Nat. Rev. Genet.* https://doi.org/10.1038/s41576-019-0144-0 (2019)

course when they are part of relevant regulatory elements.

Beyond chromatin signatures of cardiomyocyte enhancers, the late dynamic eQTLs were enriched for genes related to dilated cardiomyopathy. Moreover, the authors identified several dynamic eQTLs that were not previously known from analyses of cell lines or tissues at single time points but which have plausible links to cardiac biology. For example, single-nucleotide variants rs7633988 and rs6599234 associated with heart rhythm also showed association with dynamic expression of the sodium channel gene *SCN5A*, which is involved in heart contraction, and the cardiomyopathy-associated variant rs11124033 also associated with dynamic regulation of the heart-enriched gene *FHL2*.

Using an alternative analysis strategy, the authors identified 693 dynamic eQTLs for which the effect changes in non-linear ways throughout the differentiation time course (that is, not just a progressive increase or decrease in effect size). Several of these eQTLs are leads for further mechanistic characterization, such as the body mass index (BMI)-associated variant rs28818910, for which the effect on expression of *C15orf39* is strongest transiently in the middle of the developmental time course and was not identified through analyses of cell lines or mature tissues.

This study illustrates that capturing the time course of gene expression enables the discovery of dynamic eQTLs that would otherwise be challenging to find. Furthermore, such approaches are likely to pinpoint not only disease-relevant genes but also the particular developmental stages at which their disruption becomes pathogenic, which may provide opportunities for clinical monitoring or therapeutic intervention.

Finally, the analytical frameworks are applicable to diverse systems beyond cardiomyocyte differentiation, so could be a valuable approach to understand diverse traits and diseases.

Darren J. Burgess

ORIGINAL ARTICLE Strober, B. J. et al. Dynamic genetic regulation of gene expression during cellular differentiation. *Science* **364**, 1287–1290 (2019)

TECHNIQUE

Optoepigenetics for 3D genome engineering

Credit: Paul Paladin/Alamy

Loop engineering techniques that modulate long-range chromosomal interactions play a pivotal part in deciphering the relationship between 3D genome architecture and function. Now, Kim, Rege et al. present the light-activated dynamic looping (LADL) system, which is based on a synthetic architectural protein that rapidly induces long-range chromatin interactions in response to blue light.

The LADL system comprises two plasmids, one encoding a LADL 'anchor' and one encoding sequence-specific CRISPR guide RNAs (gRNAs) designed to target two genomic regions to be joined through loop formation. The LADL anchor is formed of an enzymatically inactive Cas9 (dCas9) that is fused to a truncated version of the CIB1 protein (CIBN; also known as transcription factor bHLH63) from *Arabidopsis thaliana*. gRNAs guide the LADL anchor to the two desired genomic anchoring sites. The gRNA-encoding plasmid also includes *CRY2*, whose protein product acts as an inducible bridging factor that joins the two anchoring sites upon activation with blue light (470 nm wavelength) through heterodimerization with CIBN.

Using mouse embryonic stem (ES) cells, the authors compared transfected cells exposed to 24 h of blue light or dark and found no differences in dCas9 and CRY2 transcript levels nor in the expression of pluripotency markers between the two conditions. This finding suggests that transfection and light induction had no impact on transgene expression or the ES cell state. To test the LADL system, the authors chose a ~800-kb-sized region around the *Klf4* and *Zfp462* genes, reasoning that loop engineering would redirect the interaction between *Klf4* and its long-range enhancer to *Zfp462*. Recruitment of the LADL system to its target locations was measured by chromatin immunoprecipitation followed by quantitative PCR (ChIP–qPCR), which confirmed the presence of dCas9–CIBN at both the *Klf4* enhancer element and the *Zfp462* promoter under dark conditions.

Blue light activation led to a doubling in intensity of the dCas9–CIBN ChIP signal at the *Zfp462* promoter and a slight signal decrease at the *Klf4* enhancer. A high-resolution map of long-range chromatin interactions generated by chromosome conformation capture carbon copy (5C) showed the formation of a new contact between *Zfp462* and the *Klf4* enhancer upon blue light illumination. The loop between *Klf4* and its enhancer remained largely unperturbed. Notably, the newly formed loop between *Zfp462* and the enhancer was detectable 4 h after the start of the light stimulus, which is substantially faster than current chemical loop engineering approaches. Finally, single-molecule RNA fluorescence in situ hybridization showed a modest increase in *Zfp462* expression.

While the approach requires improvements to increase the strength of LADL-induced contacts, the method should prove useful for 3D optoepigenetic engineering of chromatin at short time scales.

Linda Koch

ORIGINAL ARTICLE Kim, J. H. & Rege, M. et al. LADL: light-activated dynamic looping for endogenous gene expression control. *Nat. Methods* **16**, 633–639 (2019)