be exploited to bioinformatically remove contaminating RNAs that bind nonspecifically to the affinity chromatography matrix, thereby increasing the specificity of Proximity-CLIP. UV crosslinking also avoids some pitfalls of formaldehyde crosslinking, such as the crosslinking of long-range or indirect interactions.

Applying their technique to HEK293 cells inducibly expressing APEX2 fused either to a nuclear export signal or to histone H2B, Benhalevy et al. determined both the proteome and transcriptome of the cytoplasm and nucleus, respectively. Functional enrichment analysis showed that proteins biotinylated by H2B-APEX2 were involved in transcription or belonged to nuclear categories, such as 'nucleus' and 'nucleoplasm'. Moreover, the protein profiles resembled those previously reported in a study that used mass spectrometry to determine nuclear and cytoplasmic proteomes.

Transcriptome profiles of the cytoplasmic and nuclear compartments obtained using Proximity-CLIP matched RNA profiles obtained after biochemical fractionation. Furthermore, sequencing of RBP-protected fragments from both nucleus and cytoplasm revealed a footprint profile that reflected each compartment; that is, the vast majority of RBP footprints on mRNA in the cytoplasm were found on mature mRNA, whereas 43% of mRNA footprints in the nucleus resided in introns.

Taken together, Proximity-CLIP can be used to simultaneously map the compartment-specific landscape of RBPs, the transcriptome and RBP-occupied RNA loci. Its high throughput compared with imaging-based techniques makes it particularly appealing for identifying the subcellular localization of transcripts and potentially interacting RBPs.

Linda Koch

ORIGINAL ARTICLE Benhalevy, D. et al. Proximity-CLIP provides a snapshot of protein-occupied RNA elements in subcellular compartments. *Nat. Methods* **15**, 1074–1082 (2018)


Credit: FlamingoImages/iStock/Getty

In the next step, a reader module, synR, was engineered by fusing the m6A reader domain of *Streptococcus pneumoniae* DpnI to various transcriptional effector domains, namely the VP64 activation domain, the KRAB repressive domain and the chromo shadow domain of HP1a. These synR modules induced or repressed transcription according to the endogenous function of the fused transcriptional effector. To achieve more versatile targeting options for the synI module (without the need for the synthetic BS), a CRISPR-guided synI module was generated that mediated methylation of the guide RNA-defined target sites.

Finally, to model the spreading of an epigenetic mark from a nucleation site, a read–write module was constructed, consisting of the m6A reader domain and the Dam writer domain. A small-molecule inducible initiator was brought into cells together with the read–write module, and spatial propagation of m6A was monitored using the clustered reporter. This propagation circuit also enabled confirmation of the principle of epigenetic memory. In the absence of the inducing small molecule, cycling cells showed partially stable expression of the reporter over approximately ten generations.

The researchers envision that in the future this synthetic suite of chromatin regulators could be expanded to include eraser modules and be adapted to study and manipulate genome architecture and dynamically control gene expression.

Michelle Trenkmann, Associate Editor, Nature Communications

ORIGINAL ARTICLE Park, M. et al. Engineering epigenetic regulation using synthetic read-write modules. *Cell* https://doi.org/10.1016/j.cell.2018.11.002 (2019)

GWAS

Risk loci for ADHD


Credit: Lobro/Alamy

Attention deficit/hyperactivity disorder (ADHD) is a behavioural disorder that affects about 5% of children and adolescents and 2.5% of adults. Despite an estimated heritability of 70-80%, genome-wide association studies (GWAS) have so far failed to identify any common genetic variants robustly associated with ADHD. Now, a study in *Nature Genetics* reports 12 genome-wide significant loci for ADHD, which implicate biologically informative genes as important to its aetiology.

GWAS were conducted on 12 European, North American and Chinese cohorts that comprised 20,183 individuals with ADHD and 35,191 controls. Meta-analysis of these GWAS identified 304 genetic variants (from a total of 8,047,421) that exceeded the genome-wide significance threshold ($P < 5 \times 10^{-8}$). These variants represented 12 distinct loci and the associations were consistent across all 12 cohorts. The single-nucleotide polymorphism (SNP) heritability (h^2_{SNP}) was estimated to be 0.22, which is consistent with other complex traits and with figures from previous smaller ADHD studies ($h^2_{SNP} = 0.1–0.28$) and GWAS for other neurodevelopmental disorders, such as schizophrenia ($h^2_{SNP} = 0.23–0.26$).

Several of the 12 significant loci were shown to be in, or close to, genes involved in neurodevelopmental processes relevant to ADHD. For example, the *FOXP2* gene in the chromosome 7 locus is involved in synapse formation and the development of speech and learning; problems with language development and learning are common in ADHD. Similarly, the chromosome 12 locus spans *DUSP6*, whose possible role in regulating dopamine levels at synapses is consistent with the purpose of ADHD medications that act to increase the availability of synaptic dopamine.

Of 219 phenotypes tested for pairwise genetic correlation, 43 had significant genetic overlap with ADHD. In most cases, these correlations were supported by multiple related phenotypes. For example, positive correlations were observed for major depressive disorder, depressive symptoms and neuroticism. Negative correlations were observed for years of schooling and human intelligence. This genetic overlap with epidemiologically relevant phenotypes lends weight to the view that ADHD is the extreme expression of one or more continuous heritable traits.

Thus, further analysis of the loci and pathways implicated by this study might provide insight into the aetiology of not only ADHD but also other, related disorders.

Dorothy Clyde

ORIGINAL ARTICLE Demontis, D. et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat. Genet.* https://doi.org/10.1038/s41588-018-0269-7 (2018)