A161 · Investigating the impact of promoter-promoter interactions on gene regulation

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Cis-regulatory elements (CREs) coordinate transcriptional programs through interactions with transcription factors, chromatin-associated proteins, and other regulatory elements. Although candidate CREs have been extensively mapped across cell types and states, how different classes of CREs interact to collectively regulate gene expression remains less well understood.

We integrated the ENCODE Registry of candidate cis-regulatory elements (cCREs) with 3D interaction data across six deeply profiled cell lines to annotate more than 300,000 promoter-centric interactions. Nearly one-third of these interactions occurred between two promoters. Because promoters can influence neighboring gene expression through processes such as enhancer-like activity or competition for transcriptional machinery, we further characterized the properties and potential regulatory roles of these promoter-promoter (P-P) interactions.

Looking across a set of six ENCODE deeply profiled cell lines, we found that many of these P-P interactions were shared between the cell lines compared to the other P-cCRE interactions. Genes connected by P-P interactions showed greater expression correlation than randomly paired genes. Most promoters participating in P-P interactions contacted multiple other promoters, whereas relatively few formed an exclusive interaction with a single partner, suggesting organization into larger multi-promoter hubs. Ongoing analyses are examining interaction stability following acute protein depletion and shared transcription factor motifs and occupancy patterns. We also developed HUBble (hubble.moore-lab.org), an interactive resource for exploring promoter-centered 3D regulatory interactions.

Together, these findings suggest that promoter-promoter contacts represent a structured and potentially functional component of gene regulatory networks, with implications for coordinated transcriptional regulation and interpretation of promoter-targeting perturbations.

Investigating the impact of promoter-promoter interactions on gene regulation

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We integrated the ENCODE Registry of candidate cis-regulatory elements (cCREs) with 3D interaction data—including RNAPII ChIA-PET, CTCF ChIA-PET, and Hi-C—across six deeply profiled cell lines to annotate more than 300,000 promoter-centric interactions. Nearly one-third of these interactions occurred between two promoters. Because promoters can influence neighboring gene expression through processes such as enhancer-like activity or competition for transcriptional machinery, we further characterized the properties and potential regulatory roles of these promoter-promoter (P-P) interactions.

Looking across a set of six ENCODE deeply profiled cell lines, we found that many of these P-P interactions were shared between the cell lines compared to the other P-cCRE interactions (**Fig. 1A**). Genes connected by P-P interactions showed greater expression correlation than randomly paired genes (**Fig. 1B**). Most promoters participating in P-P interactions contacted multiple other promoters, whereas relatively few formed an exclusive interaction with a single partner, suggesting organization into larger multi-promoter hubs. Ongoing analyses are examining interaction stability following acute protein depletion and shared transcription factor motifs and occupancy patterns. We also developed HUBble (hubble.moore-lab.org), an interactive resource for visualizing promoter-centered 3D regulatory interactions.

Together, these findings suggest that promoter-promoter contacts represent a structured and potentially functional component of gene regulatory networks, with implications for coordinated transcriptional regulation and interpretation of promoter-targeting perturbations. Characterizing these relationships may improve our understanding of coordinated transcriptional regulation and help anticipate indirect effects of promoter-targeting perturbations, where manipulating one promoter could influence additional genes within the same regulatory neighborhood.

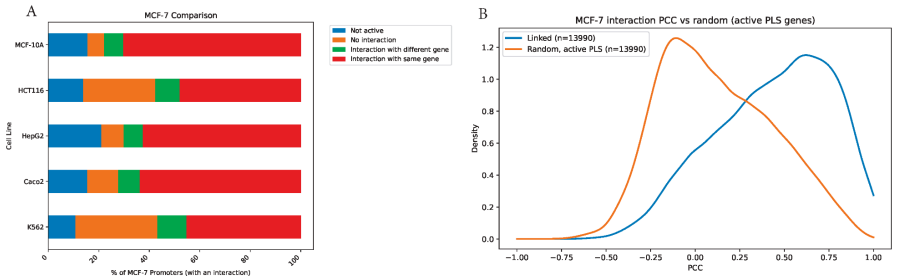

Figure 1. Promoter-centric analysis reveals many promoter-promoter (P-P) interactions that have previously been overlooked. A) Pairwise analysis of P-P interactions in MCF-7 compared to the other deeply profiled cell lines. An average of 58% of P-P interactions were observed in at least four of the six cell lines. B) Comparison of gene expression correlation between P-P linked pairs in MCF-7 (blue) and randomly selected active promoter pairs (orange).