Biased orientations of DNA motifs affecting enhancer-promoter interactions

Chromatin interactions a mechanism of enhancer-promoter associations

Known transcription factors (TFs) associated with chromatin interactions

TFs associated with chromatin interactions (brown TFs: CTCF, RAD21, SMC3, Y1, 2N-14f)

Chromatin-associated regulatory motifs

Summary

96 biased orientations (84 forward-reverse (FR) and 52 reverse-forward (RF)) of motifs that significantly affected the expression level of prospective transcriptional target genes in monocytes, T cells, HMEC, and NPC and included CTCF, cohesion (RAD21 and SMC3), Y1, and 2N-14f.

7 TFs were found to be associated with chromatin interactions. An important example is KLF4, which is associated with three-dimensional enhancer rewiring and transcriptional changes during the reprogramming of mouse embryonic fibroblasts to pluripotent stem cells (Sarnamartino et al. Nature Cell Biology 2013).

Many other TFs were also known to have chromatin-associated functions such as chromatin remodeling, chromatin accessibility, pioneer factors, and/or histone modification. These findings contribute to the study of chromatin-associated motifs involved in transcriptional regulation, chromatin interactions, regulation of chromatin, and histone modifications.

Osato N (2018) Characteristic of functional enrichment and gene expression level of human putative transcriptional target genes. BMC genomics.

Osato N (2020) Discovery of directional chromatin-associated regulatory motifs affecting human genes transcription. bioRxiv preprint, doi: https://doi.org/10.1101/290825

Comparison of expression level of putative target genes of each TF between promoter and enhancer-promoter association domain

Association rule 4 shortened at forward-reverse orientation of CTCF binding sites showed the most significant difference of distribution expression level of target genes.

Enhancers affect the expression level of genes significantly.

Osato N, BMC Genomics 2018

Transcriptional target genes

Randomly selected genes

Transcription factors (TF)

Functional enrichments of native and randomized transcriptional target genes using ChIP-seq data (upper) and Dnase-DGF lower. Native target genes included the most functional enrichments.

Comparison with chromatin interaction data

Correlation of expression level of nearby genes

The table show the number of biased orientations of DNA motifs, where a significantly higher ratio of EPIs that were predicted based on an enhancer-promoter association (EPA) domain (i) overlapped with HiChIP chromatin interactions than the other types of EPA domain (ii) and (iii) in T cells.

Transcriptional target genes tend to include similar function of genes

Biased orientations of motifs found in four cell types

Expression level of putative transcriptional target genes

Comparison of biased orientations of DNA motif sequences

Transcription factor and extended regions for enhancer-promoter association (EPA) (McLean et al. 2018). Transcription start site of each gene is indicated as an arrow.

Association rule 3 was the longest among the four criteria, it showed the lowest number of functional enrichments in the seven cell types. Association rule 4 was the highest.

Enhancer-promoter association (EPA) shortened at CTCF binding sites increased the normalized numbers of functional enrichments. Forward-reverse orientation of CTCF binding sites are important to form chromatin interaction loop and increased functional enrichments of putative transcriptional target genes in seven cell types.

Discovery of directional chromatin-associated regulatory motifs affecting human gene transcription

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ChIP-seq Enhancer gene promoters.

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Graphical Abstract

Example of CBS Orientation-Dependent Topological

For example, there is a CBS pair in the reverse-forward orientation exist in >60% neighboring TAD boundaries (opposite topological looping and thus appears to function as a mechanism of domain1 and CBS8/9 in the reverse orientation of domain2 in which the inter-domain1 and CBS in the reverse orientation establish new long-range chromatin-looping interactions. The CBS4 (3-9) and CTCF binding polarity determines chromatin looping.

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