**Literature**

*Intra-TAD coordination*

- Chromosomal Contact PermitsTranscription between Coregulated Genes (Fanucchi et al. 2013)

- Functional gene groups are concentrated within chromosomes, among chromosomes and in the nuclear space of the human genome (Thévenin et al. 2014)

- Topologically associated domains enriched for lineage-specific genes reveal expression-dependent nuclear topologies during myogenesis. (Neems et al. 2016)

- Spatial partitioning of the regulatory landscape of the X-inactivation centre (Nora et al. 2012)

- Distinct structural transitions of chromatin topological domains correlate with coordinated hormone-induced gene regulation (Le Dily et al. 2014)

- TADs as modular and dynamic units for gene regulation by hormones (Le Dily and Beato 2015)

- Revealing Gene Function and Transcription Relationship by Reconstructing Gene-Level Chromatin Interaction (Liu et al. 2019)

*Absence of coordination*

- Highly rearranged chromosomes reveal uncoupling between genome topology and gene expression (Helm et al. 2019)

**RNA-seq datasets**

Gene expression data (RSEM ) were retrieved from The Cancer Genome Atlas (TCGA; *ask Marco TCGA\_transcriptome\_Oct2016*).

**RNA-seq data processing and differential expression analysis**

Differential expression analysis was conducted on R with the *limma* package (*lmFit*, *eBayes*, functions; Ritchie et al. 2015). We retrieve the log fold-change (logFC) values from the table returned by the *topTable* function, and averaged the mean logFC values of the genes for each TAD.

**Hi-C datasets**

*=> Yuanlong*

**Hi-C data processing and TAD calling**

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**TAD list filtering**

TADs containing at least 3 genes but not more genes than the 99-th percentile were retained for further analyses.

**Log fold-change empirical p-values**

100’000 permutations were generated following the procedure described in Le Dily et al. (2014). Gene-to-TAD assignment was shuffled within 5 equal-sized classes generated based on the expression level (allowing to maintain an equivalent gene expression per TAD). To account for gene length, scaled estimates of gene expression data (instead of RSEM) were used to create the classes of gene expression. The TAD mean logFC was then computed for each of the permutation.

Empirical p-values were calculated as (# abs(permut. logFC) >= abs(obs. logFC) + 1)/(# permut + 1).

**Intra-TAD correlation empirical p-values**

Random data were generated according to the following strategy: for each TAD of each Hi-C data, we selected the same amount of closest genes as contained in the TAD. Then, we computed the average of the pairwise Pearson’s correlations between the TAD genes and the sampled genes.

Empirical p-values were computed as (# permut. corr values >= obs. corr + 1)/(# permut + 1).

**Combined p-values**

The logFC empirical p-values and the intra-TAD correlation empirical p-values were combined using the Stouffer’s method (Stouffer et al. 1949; one-sided), and adjusted following the Benjamini-Hochberg method (as implemented by the *p.adjust* R function).

**False discovery rate (FDR) analysis**

The FDR analysis was inspired by the analyses presented in Tusher et al. (2001).

*Mean TAD logFC*

For various thresholds, the FDR is calculated as mean # permut. abs(logFC) >= threshold / # obs. abs(logFC) >= threshold. The thresholds ranged from 0 to 5 by 0.05.

*Intra-TAD correlations*

For various thresholds, the FDR is calculated as mean # permut. intra-TAD corr. >= threshold / # obs. intra-TAD corr. >= threshold. The thresholds ranged from 0 to 1 by 0.01.

Then, for a given FDR threshold, the mean logFC (resp. intra-TAD correlation) threshold was determined as the smallest value that yields a FDR smaller or equal the given FDR.

**References**

Stouffer, S.A., Suchman, E.A., DeVinney, L.C., Star, S.A. & Williams, R.M. Jr. 1949. The American Soldier, Vol. 1: Adjustment During Army Life. Princeton University Press, Princeton.