Promoter-anchored chromatin interactions predicted from genetic analysis of epigenomic data

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Introduction

- Promoter-anchored chromatin interaction (PAI) is essential to understand the transcriptional regulation and the genetic regulatory mechanisms underpinning complex trait variation[1].
- Current high-throughput assays for detecting PAI are not scalable to population-based cohorts because of the complexity of generating a DNA library and extremely high sequencing depth to achieve high detection resolution[2].

Materials and Methods

- We proposed an analytical approach to predict chromatin interaction using summary level methylation quantitative trait locus (mQTL) data.
- Our analytical approach relies on the SMR (summary-data–based Mendelian randomization) & HEIDI (heterogeneity in dependent instruments) method[3] to detect the association between DNAm levels of two CpG sites due to the same set of genetic variants.
- The summary-level blood mQTL data were from a meta-analysis of LBC and BSGS cohort (n=1,980).

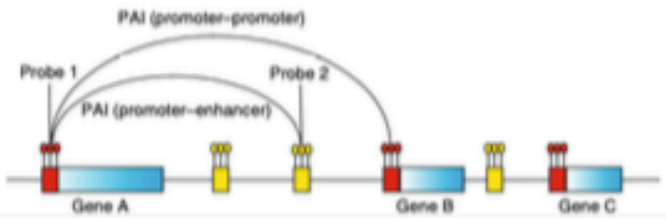

Figure 1 A schematic of the PAI analysis.

Results

- We identified 34,797 PAIs for the promoter regions of 4,617 genes.
- The predicted PAIs show strong overlap with the chromatin contacts identified by previous experimental assays.

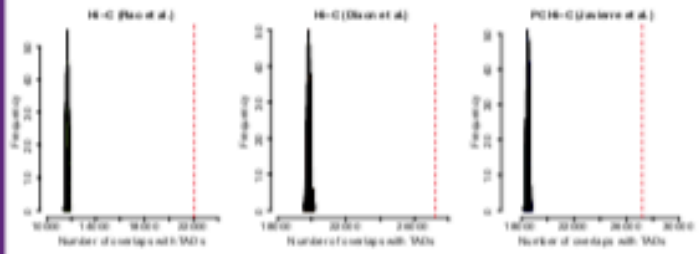

Figure 2 Overlaps of the predicted PAIs with topologically associating domains (TADs) identified by **a** Rao et al.[4], **b** Dixon et al.[5] and **c** Javierre et al.[1] using Hi-C and promoter-captured Hi-C (PCHi-C).

- The predicted interactions from our method are more enriched in the PCHi-C loops[6] compared to other prediction methods.

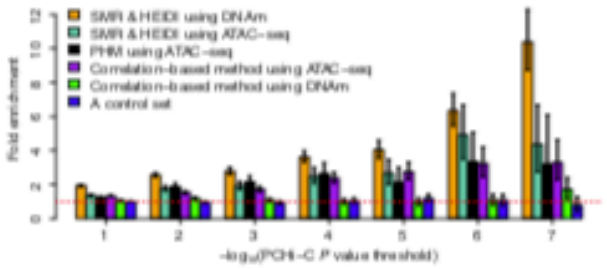

Figure 3 Enrichment of the predicted interactions in the significant PCHi-C loops[6] defined based on a range of P-value thresholds. The fold enrichment value was computed by a 2 × 2 contingency table and the horizontal red dashed line indicates no enrichment.

Results

- The promoter-interacting DNAm sites are enriched in enhancers or near expression QTLs.
- Genes whose promoters are involved in PAIs are more actively expressed, and gene pairs with promoter-promoter interactions are enriched for co-expression.

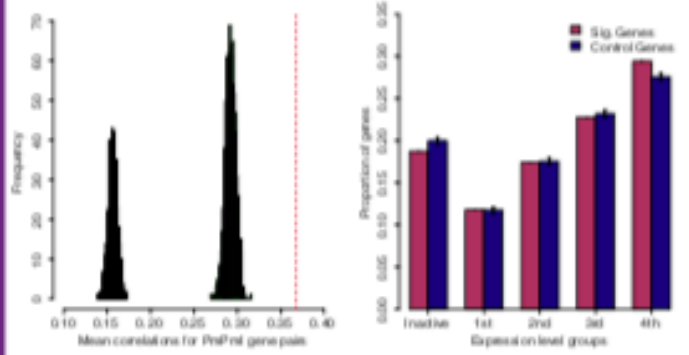

Figure 4 Mean Pearson correlation of expression levels for gene pairs whose promoters were involved in promoter-promoter interaction and proportion of promoter-PAI genes in gene activity groups.

Conclusions

- We propose an analytical approach that uses the summary-level data from cohort-based mQTL studies to predict PAIs.
- The predicted PAIs show strong overlap with the chromatin contacts identified by experimental assays and outperformed other prediction methods.
- This study demonstrates the use of mQTL data to predict PAIs and provides insights into the role of PAIs in complex trait variation.

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Publication

Wu Y. et al., Nature Communications 11, 2061 (2020).

References

1. Javierre, B.M. et al., Cell 167, 1369–1384.e19 (2016).
2. Hnisz, D. et al., Methods 58, 268–276 (2012).
3. Zhu, Z. et al., Nat Genet 48, 481–7 (2016).
4. Rao, S.S. et al., Cell 159, 1665–1680 (2014).
5. Dixon, J.R. et al., Nature 485, 376–380 (2012).
6. Jung, I. et al., Nat. Genet. 51, 1442–1449 (2019).