Measuring DNA Binding Configurations at Single Cell Resolution Using Deep Sequencing

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Abstract

Genetic variation in non-coding regulatory regions accounts for a significant fraction of changes in gene expression among individuals from the same species. However, without a 'regulatory code' that informs us how DNA sequences determine expression levels, we cannot predict which sequence changes will affect expression, by how much, and by what mechanism. To address this challenge, we developed a high-throughput method for constructing libraries of thousands of fully designed regulatory sequences and measuring their DNA binding configurations and expression levels in parallel, within a single experiment, and at single cell resolution. Using this ~1000-fold increase in the scale with which we can study the effect of sequence on DNA binding and expression, we designed and measured libraries in which the location, number, affinity and organization of different types of regulatory elements has been systematically perturbed. Our results provide several new insights into principles of gene regulation, bringing us closer towards a mechanistic and quantitative understanding of which how expression levels are encoded in DNA sequence.