Characterizing the Human Transcriptional Landscape: The Allele Binding Cooperativity Test

Konrad Karczewski*, Maya Kasowski, Fabian Grubert, Manoj Hariharan, Mark Gerstein, Jan Korbel, Russ Altman, Michael Snyder

* Stanford University, konradjk@stanford.edu

Regulation of gene expression at the transcriptional level is achieved by binding of transcription factors to their target promoter sequences. While there is often a single most important factor for the regulation of a certain gene in a certain condition (such as NFκB in inflammatory response), in reality, transcription is controlled by a combination of factors, each contributing to switching transcription on or off in a given condition. Here, we develop a method to discover potential interactors of a given transcription factor by analysis of differences in ChIP-Seq binding data in 10 individuals. Using this new test, the Allele Binding Cooperativity (ABC) test, we predict a number of transcription factors potentially associated with NFκB in a search of the JASPAR motif database. Although some factors have been suggested previously to work with NFκB, many have not. We then validate these predictions by ChIP-Seq of these putative interacting factors. In addition, using results from the ABC test, we implement classifier and regression methods to characterize transcription factor binding from promoter sequence data across loci. We use these techniques, coupled with experimental validation, to characterize the combinatorial model of transcriptional regulation.