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High-resolution mapping of transcription factor binding sites on native chromatin

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Sequence-specific DNA-binding proteins including transcription factors (TFs) are key determinants of gene regulation and chromatin architecture. Formaldehyde cross-linking and sonication followed by chromatin immunoprecipitation and sequencing (X-ChIP-seq) is the most widely used technique for genome-wide profiling of protein binding sites. However, there are many issues associated with X-ChIP including low resolution and poor specificity and sensitivity. Here, we implement native (i.e., without cross-linking) ChIP of micrococcal nuclease-digested chromatin followed by paired-end sequencing (N-ChIP-seq) for mapping binding sites of the structurally distinct budding yeast TFs Abf1 and Reb1. N-ChIP-seq reproducibly recovers Abf1 and Reb1 binding sites with higher specificity and sensitivity than other profiling methods and identifies both previously characterized and novel sites. Altering N-ChIP-seq conditions allows flexibility in modulating specificity and sensitivity of binding site detection. Further, unlike X-ChIP methods, N-ChIP-seq is not biased toward identifying sites in accessible chromatin. Taken together, these results suggest that N-ChIP-seq outperforms current X-ChIP methodologies for genome-wide profiling of TF binding sites.

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